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# BRITISH MEDICAL JOURNAL

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SATURDAY APRIL 21 1951

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 21 1951

# DEGENERATION, NECROSIS, AND FIBROSIS IN THE LIVER*

BY

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*Professor of Pathology, Postgraduate Medical School of London*

[WITH PHOTOGRAVURE PLATE]

## LECTURE I

In these lectures I have drawn as far as possible upon pathological studies in the human subject. The brilliance of experimental work and speculation within the past decade has opened a new chapter in the pathology of degenerative, necrotic, and fibrotic changes in the liver, and there has been built up a mass of material the significance of which I think must now be weighed against our findings in human pathology. The contributions of the rat have been notable and stimulating, but there must be some doubt to what extent findings in this animal, which has been the subject of most of the experimental work, can be applied to the elucidation of human pathological problems. It is my proposal to inquire into this in a certain limited field and to rely in the main upon my own observations.

### Two Sets of Observations

Looking broadly over these changes in knowledge of the pathology of liver disease two sets of observations challenge our notice. The first is the finding that degenerative conditions, and ultimately fibrosis of the liver, may be produced by dietetic means, and the second the fuller appreciation of the pathology of infective hepatitis and its relationship to necrosis and fibrosis of the liver. We find that two apparently different processes lead us to the common ground of liver cell death—the one a matter of nutrition and therefore susceptible of biochemical analysis, the other an infective process (for "catarrhal jaundice" has been thoroughly demonstrated to behave as an infective disease, and the closely akin condition—which is histologically identical—of "homologous serum" or "syringe" jaundice is almost certainly of this nature). This infective jaundice, as I shall presume to call it, is generally a mild disease, but it is all the time shadowed by the menacing condition of acute atrophy or massive necrosis—a relationship which was obvious enough to Bright and Addison (1836), but which was rather forgotten in the latter years of the last century and the earlier ones of this—largely, I believe, through a temporary diminution in the incidence of the graver form, but chiefly through the mistaken teaching of Virchow.

Of that legendary figure it might be said, as was said of Laurence Sterne, "Great were his faults, but glorious was his flame"; for in the field I am about to traverse his work has been the basis of two important misconceptions: first, concerning the nature of fatty degeneration, and, secondly, concerning the nature of simple jaundice.

### Influence of Diet

Through the work on disease of the liver due to diet run two main themes, or so it seems to me. First, that dietetically produced fatty infiltration of the liver leads ultimately to cirrhosis (or "diffuse fibrosis," as Himsworth prefers to call it) and that this condition can be prevented by amino-acids with labile methyl groups such as methionine, or by choline. If it be true that cirrhosis is caused by fatty infiltration, then it follows that the giving of these "lipotropic" substances should prevent the disease. Secondly, that massive liver necrosis without fatty infiltration can be produced by protein deficiency, due *au fond* to lack of the organic sulphur-containing amino-acid cystine (Daft, *et al.*, 1942; Hock and Fink, 1943; Himsworth, *et al.*, 1945). These differences in causation and distribution of the lesion have been found to produce dissimilar and characteristic fibroses in the animals' livers, so that in the one case (that of fatty cirrhosis) a monolobular type of fibrosis results and in the other (massive necrosis) a polylobular coarse scarring.

If these findings hold good in human pathology the attractive suggestion emerges that we can distinguish at necropsy the different aetiological processes which have led to what we loosely call cirrhosis—the picture of which we all know to be varied enough—and, what is of more importance, they should point the way to their prevention by dietetic measures.

The first problem I wish to examine is the question whether fatty infiltration causes cirrhosis; the second, to what extent valid distinctions can be drawn between the different fibroses of the liver in man.

It may be said that pathologists generally have long been inclined to the view that the larger nodular form

*Humphry Davy Rolleston Lectures delivered at the Royal College of Physicians of London on June 20 and 22, 1950.

of cirrhosis, which often receives the special name of nodular hyperplasia, probably arises as a result of subacute necrosis (or subacute atrophy, to give it an older and less accurate term) and represents attempts at regeneration in a liver damaged by chemical poisons, or that it arises in recovery from acute atrophy; and that the finer forms of fibrosis are the result of long-continued slow destruction of liver cells.

### Fatty Change in the Liver Cell

To consider the relationship of fatty infiltration to ultimate fibrosis we have to inquire what causes a liver cell to become fatty and how such a change can lead to fibrosis. Is the fatty cell to be assumed to die and to give place to fibrous tissue—for fibrosis as a pathological process in parenchymatous organs with high oxygen requirements is usually a replacement fibrosis? If this be the chain of events, then fatty infiltration precedes necrosis and cell necrosis leads to fibrosis. On the other hand, the presence of fat in the liver cell may merely indicate that its metabolism is disordered and it may be the result and not the cause of events which lead in the long run to the death of the liver cell.

The causes of fatty infiltration of the liver are still imperfectly understood, and I regret to say very often wrongly taught. Textbooks have not yet completely forgotten the teachings of Virchow that fatty change of two types which are histologically distinguishable may commonly occur—fatty degeneration and fatty infiltration—the former being a transformation of cell protein into fat, the latter an accumulation of fat brought to the tissues from the outside by the blood.

The liver, in common with most other cells of the body, ordinarily does not show any fat when stained by the usual histological methods, but on chemical extraction yields between 2 and 3% of its wet weight of fat. This is a cellular constituent existing independent of the body's state of nutrition, and is not removed in starvation. Such fat has been called *élément constant*, or, since it is not stainable, "masked fat," and is either in combination or in some physical state in which it does not react to fat stains. As it can be demonstrated chemically it is conceivable that an analogous chemical decomposition can be brought about in the body in disease and the fat be rendered visible or unmasked. I believe this conception to be mainly hypothetical; for though certain powerful agents—such as *Clostridium welchii* lecithinase ("$\alpha$-toxin"), which will cause the clouding of serum by the decomposition of its phospholipids—will produce *in vitro* a similar change in the protoplasm of liver cells (as Dr. B. K. Aikat has demonstrated for me), yet there is little evidence of such a process occurring in life, and in any case the quantity of fat set free is minimal. If such a change does take place it takes place without an increase in the chemically extractable fat, since it is simply a process of freeing from combination fat that is already there. If, however, the appearance of visible fat is accompanied by an increase in actual quantity, then it follows that fat has entered the cell from the outside. All the evidence I have found in the course of a good deal of investigation of this question goes to show that this is what occurs in fatty change in the liver cell.

If we therefore accept, as I claim we must, that the change in question is always a true infiltration, several things follow which bear upon its cause. First, the fat in the liver cell must be brought by the blood, and hence if no fat can get to the blood none can get to the liver cells. Fat can reach the blood from two sources—food or the body's own reserves. If neither of these is available there can be no fatty liver. This fundamental truth was demonstrated by Lebedev as long ago as 1881, when he found that a patient in an extreme state of emaciation, who died from phosphorus poisoning, failed to show the fatty liver which is so classical a finding in this form of poisoning. It is remarkable how often this simple fact is neglected. But even more neglected is the corollary that there is a quantitative relationship between fat available for transport and the degree to which it infiltrates the liver.

### Some Experimental Work

In 1931 I became interested in the fatty change in the liver found in infants dying from "summer diarrhoea." It seemed anomalous that this exhausting and emaciating disease should be associated with an excess of fat in this organ. It had, however, been observed by Mottram in 1909 that starvation could under certain circumstances cause fatty infiltration of the liver. I thought it probable that this might be the cause of the infiltration found in the cases I have mentioned and also in a variety of other conditions. I therefore carried out some experiments upon rats and rabbits which were prevented from feeding but were allowed water. It was apparent at once that under these conditions the animals developed considerable quantities of fat in their livers, and this could be shown to be a real increase by chemical estimation. The further fact emerged that when the total fat in the animal's body was estimated, by saponifying the whole carcass (apart from the liver), a correlation was found between the

TABLE I.—*Animals Fasting from 30 to 60 Hours*

| Liver Fat % | Body Fat % | Liver Fat % | Body Fat % |
|---|---|---|---|
| 2·7 | 2·0 | 3·9 | 8·0 |
| 3·0 | 1·7 | 4·4 | 6·0 |
| 3·2 | 2·6 | 4·6 | 8·7 |
| 3·4 | 5·0 | 5·7 | 8·8 |
| 3·75 | 5·5 | 6·5 | 15·5 |
| 3·9 | 8·0 | | |

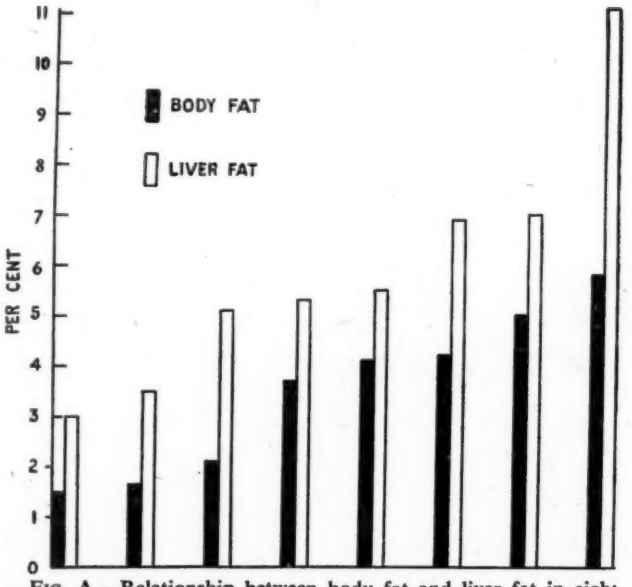


FIG. A.—Relationship between body fat and liver fat in eight guinea-pigs poisoned with phosphorus. The dependence of the degree of fatty infiltration of the liver upon the quantity of depot fat is clearly shown. The normal fat content of the guinea-pig's liver is about 2.5% of the wet weight.

two quantities (Table I). An animal with much depot fat in its body developed a heavier fatty infiltration of the liver than an animal with less fat. It looked as if the stimulus of starvation brought into being the mechanism for the mobilization of the body's reserves, and that this was not capable of delicate adjustment to metabolic requirements but affected all the fat-storing cells so that they went into action together, and the more there were of them the more fat was thrown into the circulation and reached the liver. This fat being mobilized in excess of current requirements, it accumulated in the liver cells, the extent of accumulation depending upon the extent of the mobilizable reserves. The animals (rats) at the same time developed ketosis and ketonuria, indicating a breakdown of fat in excess of the body's requirements. The same phenomenon may be seen in fatty infiltration induced by other means—for example, by phosphorus poisoning (Fig. A).

A convincing demonstration of the source of the liver fat was provided by these experiments, and the same reasoning can be applied to man, in whom I shall demonstrate it. A distinguishing feature between the essential (invisible), combined, and irreducible fat of the cell and that in the storage depots is their different abilities to combine with iodine. This is known as the "iodine value," and it is a measure of the unsaturation of the fat. The iodine value of the essential fat of the human liver cell is about 110–115 and that of the body's fat depots, which is derived from the food, is about 55–60. Now if the fat appearing in the liver cell, either in starvation or in any pathological process, comes from the depots it follows that the iodine value of the mixed fat of the cell will be lowered in proportion to the amount of low-iodine-value fat which infiltrates it. It is therefore possible, as was pointed out by Imrie, to construct a curve giving the theoretical iodine value for any quantity of fat in the cell. If the resulting figures fit this curve, then the reasoning that the fat reaching the liver comes from the animal's storage depots is correct. This was the case in the experiments I have just described. It is also true for human livers taken without selection in the post-mortem room (Fig. B).

If we accept the evidence so far adduced that fatty disease in the liver cell is a disturbance of the metabolism of transported fat we may ask: What are the proximate factors which lead to this condition—which is so common a finding in the post-mortem room?

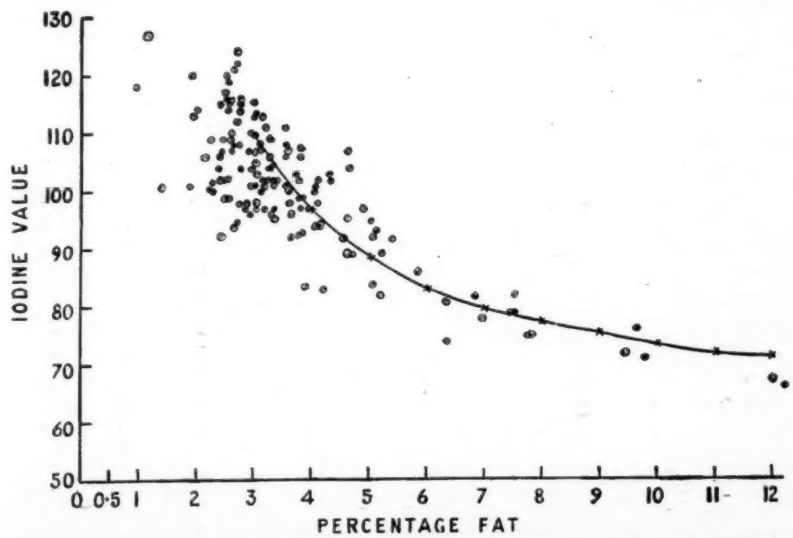


FIG. B.—Human livers (150 cases) taken at random. Actual and theoretical (continuous curve) relation of fat content and iodine value.

## Causes of Fatty Liver

Our pathological experience points to certain general causes, which may of course act together:

*Anoxia.*—One can produce fatty infiltration in the organs of an animal by the simple process of bleeding. Here, and in the severe anaemias in man, we assume that fat comes to the cell in the ordinary way, but owing to lack of oxygen its utilization is slowed, and so it accumulates in the cell's protoplasm.

*Toxaemias: Bacterial and Chemical.*—Here again we assume that the fat accumulates in the cell because of some interference with the cell's metabolism which prevents its utilization.

*General Metabolic Causes.*—Here, in some cases at any rate, we are dealing with a different mechanism. The cell may be healthy, but it receives more fat than it can deal with. This I have put forward as the explanation of the fatty infiltration in starvation, and it involves the mechanism by which fat is mobilized from the adipose tissues. That mechanism may be the ketogenic pituitary hormone which stimulates fat mobilization, or there may be others.

TABLE II.—*Analysis of Possible Causal Factors in Their Relationship to the Fat Content of the Liver in 150 Cases from the Post-mortem Room in Which Chemical Estimations were Made*

| Factor | No. of Cases in which Present | Mean Fat Content of Livers (%) |
|---|---|---|
| Starvation | 36 | 5·3 |
| Malignant disease | 22 | 5·0* |
| Large fat depots | 53 | 4·0 |
| Toxaemia (except tuberculosis) | 63 | 4·2 |
| Chronic phthisis | 13 | 4·2 |
| Pyrexia | 78 | 3·8 |
| Cardiac failure | 31 | 3·2 |
| Approximate normal food intake | 29 | 2·8 |
| Marked emaciation | 17 | 2·8 |
| Sudden death | 9 | 2·9 |

* If two cases of alimentary carcinoma with persistent vomiting and high liver fat contents (20·3% and 9·67%) are excluded, the mean liver fat content becomes 4·3%.

Leaving the general causes, and seeking the proximate causes from the point of view of the pathologist, if we take a number of unselected livers from the post-mortem room and submit them to chemical analysis we find the presence of excess of fat to be an extremely capricious phenomenon. In a series of 150 cases in which this has been done I have tried to correlate an excess of fat with a number of possible causes, and the result is shown in Table II.

Although such a method has obvious fallacies, from the overlapping of the factors considered, it will be seen that at the top of my list comes the influence of a period of inanition preceding death. This was judged by clinical histories obtained from sisters and nurses and by the content of the alimentary canal after death — rough-and-ready criteria, I would be the first to admit. But it seems that there is something in it, for if the cases are subdivided according to the estimated degree of starvation (Fig. C) a general correlation between this factor and the extent of the fatty infiltration will be found. It is only fair to state that the results are really

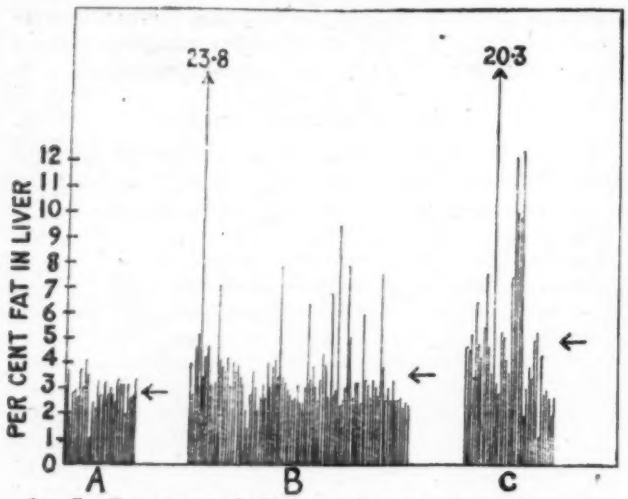


FIG. C.—Fat content of 150 livers taken at random and grouped according to the degree of ante-mortem starvation. A=approximately normal food intake. B=somewhat diminished food intake. C=markedly diminished food intake. The mean for each group is indicated by the horizontal arrow. In calculating the means the two exceptional cases (with 23.8 and 20.3% of fat) have been omitted.

to some extent biased against the view that starvation is the operative factor, since group C, with a maximum of starvation, is bound to contain a certain number of individuals in advanced emaciation in whom the fat reserves are depleted and the capacity for mobilizing fat correspondingly low.

### Fatty Infiltration and Cirrhosis

Up to now I have been dealing with the fatty liver as a general phenomenon and without specific reference to its association with cirrhosis. From what has been said the general conclusion is that fatty infiltration is a common condition apt to affect the liver cell under a variety of circumstances. The cell becomes fatty by an accumulation from the outside, and the amount of ingoing fat is determined by the amount coming to the liver cell by the blood; this, in the absence of immediately available food fat, is limited by the size of the storage depots. The evidence is in favour of the storage depots as the source of fat; and this is also in keeping with my findings in other organs (Dible, 1939).

Now let us turn to the direct evidence that fatty infiltration is a cause of cirrhosis. This view rests mainly upon dietetic experiments on the rat, in which animal fatty infiltration is produced by dietary means and is followed by changes of cirrhosis. It is important to know how severe must be the fatty infiltration and for how long it must operate to produce this result. According to Himsworth the fat content of the liver in rats needs to be of the order of 30% to produce the first indication of fibrosis within 100 days, whilst a fat content of 15% may not produce similar indications for over 300 days. Now, these are very large quantities and very considerable times, during which the animal suffers great metabolic disturbance. In the analysis of over 150 unselected livers from the post-mortem room, 95 of which showed some excess of fat, only one was found with a quantity as great as 30% and only two others with quantities in excess of 15%, so that amounts of this order are quite exceptional in man. I do not know how legitimate it is, over this matter, to relate the periods for rats to equivalent periods for man on the basis of the expectation of life of the two species—as is commonly done in regard to malignant disease—but if this be done the 100 days become the equivalent of seven to eight years, and 300 days the equivalent of about 20 years. I know of no condition in man in which such excessive quantities of fat are found in the liver for such periods of time.

It may be said that the cirrhotic liver is frequently a fatty liver, and with this I would agree, but it is quite another thing to say that this is the cause of the cirrhosis, and I would add that more than half of the livers of all patients coming to necropsy show an excess of fat. In the group of cases I have just discussed there were seven individuals whose livers contained 10% of fat, or more. Only one of these showed hepatic fibrosis: which is rather less than would be expected from pure chance association of conditions having the incidence, in the post-mortem room, of cirrhosis and fatty change of this order.

To find out if there is a constant association between an excess of fat and established cirrhosis I have been through all the post-mortem records of the British Post-graduate Medical School from the year 1939 to the present, and have examined the clinical histories and also the histology of the livers of all those cases in which hepatic "fibrosis" or "cirrhosis" was recorded. These, therefore, are cases in which this diagnosis was made by a competent pathologist. The total number is 121 (excluding infants), which represents about 2.5% of all necropsies in this period. These fibrotic livers can be classified into the following groups:

| | | | |
|---|---|---|---|
| Portal cirrhosis .. | 80 | Cardiac and portal .. | 4 |
| Cardiac cirrhosis .. | 16 | Syphilitic scarring .. | 4 |
| Biliary cirrhosis .. | 13 | Doubtful .. .. | 4 |

In all the cases in the first and largest group, which is the one which concerns us in this problem, I have looked for microscopical evidence of an excess of fat, excluding only those in which the cirrhosis was known or considered upon good evidence to have been a sequel to a previous acute hepatitis and might therefore be regarded as of different aetiology from the common cryptogenic portal cirrhosis.

*Cirrhotic Livers Examined for Fat (69)*

No. with increased fat: 30 (males 17, females 13; average age 59)
„ without „ „ 39 ( „ 27, „ 12; „ „ 60)

These results go to show that in more than half of the cases of cirrhosis coming to necropsy there is no marked excess of fat in the liver cells. But, it may be objected, it is possible for a fatty liver to have been present at an earlier stage and for this condition to have retrogressed as the disease advanced. I do not think this line of criticism is tenable, because in many of the cases included in this series the cirrhosis was clearly at an early stage. The patients did not all die from cirrhosis, or even from a disease connected with their cirrhosis, but from a diversity of causes such as malignant disease of another organ, accident, or operation, and in many the fibrotic liver was an unexpected finding at the post-mortem examination and had not given rise to any recorded symptoms during life. We have had, moreover, an opportunity of examining by biopsy a now considerable number of livers at different and in some cases early stages of the disease, and in these the proportion of fatty livers is even lower.

It remains to say a word about two other sets of observations which may be thought to bear differently upon the problem. One is the existence of fatty liver disease of infancy (Waterlow, 1948) in certain tropical countries, in which there is also a high incidence of

cirrhosis amongst the adult natives. There are strong reasons for believing the infantile disease to be one of nutrition: it appears to be a condition of failure of the liver cell, for lack of certain chemical substances, to get rid of fat, so that its accumulation is an indication of liver-cell damage and not its cause. I have read the clinical reports and failed to find any mention of ketosis, which suggests that the fat is accumulating and not being metabolized. This therefore seems to be a disease of fat transport—an excess reaching the cell and the cell failing to get rid of it. The other of these observations is the occurrence of heavy fatty infiltration of the liver in adults who have suffered from certain gastro-intestinal maladies, among which I have encountered cases of polyposis coli, ulcerative colitis, gastro-colic fistula, and gastro-ileal fistula. In some of these conditions liver fibrosis has been described. Their cause of production may be similar to that operative in the infantile disease, but, interesting as they are, their bearing on the aetiology of common cirrhosis in general does not seem great.

I conclude, therefore, that in the cirrhotic liver of man there is a lack of pathological evidence which would permit us to presume that this condition is a late effect of prolonged and heavy fatty infiltration. It is my opinion that the fat which is not infrequently seen in the fibrotic liver in man accumulates there as a result of his disease and, so far as causes in the liver itself are concerned, of circulatory and metabolic changes to which the disease gives rise. This is tantamount to saying that the cirrhotic liver accumulates fat from causes similar to those which produce this change in the non-cirrhotic, with the possible difference that the cirrhotic liver is less able to get rid of fat than is the non-cirrhotic. To go into this question further I have picked out the cases in my series in which excess of fat is really a marked feature, to see if they give us any help with the problem.

### The Association of Fatty Infiltration and Cirrhosis

A notable fact about the group analysed in Table III is that in many of them one sees the operation of factors which, as I have previously pointed out, promote fatty infiltration under any condition—viz., obesity, alcoholism, diabetes, acute infection. The incidence of the factor of starvation in this group was not explored: it might well have operated in some of the cases. Two other rather unexpected facts emerge: first, that the average age is if anything slightly over that of the cirrhotic group as a whole (58.5 years)—another bit of evidence against a fatty liver in earlier life becoming a cirrhotic one later on; and, secondly, that the females outnumber the males by ten to three—a very striking reversal of general experience and of the figures for my whole series, which consists of 51 males and 29 females. The number is, of course, too small for me to make safe deductions, but, so far as it goes, it suggests that in Hammersmith Hospital a fatty liver in cirrhotics is linked with the female sex.

TABLE III.—*Analysis of Markedly Fatty Cirrhotic Livers*

| Case No. | Age | Sex | Weight (g.) | Notes |
|---|---|---|---|---|
| 394 | 80 | M | 1,400 | Rather coarse |
| 612 | 38 | F | 1,960 | Monolobular. Alcoholic. Infection. Obese |
| 669 | 54 | F | 2,605 | Fine cirrhosis. Congestive. Obese |
| 856 | 68 | F | 1,005 | Almost unilobular, active. Obese |
| 1542 | 43 | F | 2,600 | Fine cirrhosis. Alcoholic. Obese |
| 1697 | 54 | F | 1,780 | Coarse cirrhosis. Pneumonia. Obese |
| 1774 | 53 | F | 1,400 | Coarse. Meningitis. Obese |
| 2849 | 66 | F | Small | Fine multilobular. Lobar pneumonia |
| 4148 | 76 | M | — | Coarse multilobular. Hepatoma |
| 4606 | 60 | F | 1,120 | Fine portal plus mild cardiac |
| 4871 | 70 | F | 1,680 | ,, ,, ,, ,, ,, Pyonephrosis |
| 4908 | 67 | M | 1,300 | Fine multilobular. Alcoholic. Syphilitic |
| 4921 | 62 | F | 1,215 | Coarse. Alcoholic. Diabetic. Obese |
| Mean | 61 | | 1,582 | |

Finally, if these views are correct and fatty infiltration does not cause cirrhosis in man, clearly there can be no anatomical form of cirrhosis due to this cause.

## LECTURE II

Having dealt with the possible importance of fatty infiltration as a cause of cirrhosis in this country, I propose in this second lecture to produce the evidence that there is one picture of portal cirrhosis, and that this is essentially the same whether due to a known cause—that is, sequential to an acute hepatitis—or whether it is cryptogenic and develops without a known previous attack of hepatitis. That the pathological appearances in a random series of livers with portal cirrhosis differ vastly is beyond dispute; but if the attempt be made to find a constant correlation between a certain pathological picture and a certain aetiological agent the attempt fails. The different pictures seen in portal cirrhosis are aspects and stages in a process which varies in severity and acts on an organ in which the response is not always precisely the same.

Before dealing with portal cirrhosis, about which the discussion centres, a little may be said to clear away other types of cirrhosis and to indicate their characteristic features and to stress points of similarity and difference between them and portal cirrhosis.

### Biliary Cirrhosis

This condition, as is well known, results from blockage of the bile ducts, leading to obstructive jaundice. The causes of obstruction are various, and an element of infection may be added which modifies but does not very much change the fundamental picture. The resulting effects depend upon the completeness of the obstruction. Where this is complete there is in the beginning monolobular fibrosis of the portal tracts with retention of bile, central necrosis of the liver lobules with pigmentation of the cells, and frequently scattered areas of "bile necrosis" in the parenchyma. Where the obstruction is incomplete, monolobular fibrosis may develop without central necrosis and there may be very much less pigmentation. These may be added as the condition progresses. There is no doubt that a good deal of the necrosis which is sometimes a marked feature of these livers at necropsy is agonal, or of post-mortem development, since it is not so striking in biopsy specimens. As the condition advances, the bands of fibrous tissue become joined, and with the development of hyperplastic nodules a picture may in time be reached which superficially resembles portal cirrhosis. A distinguishing feature, however, is the presence of an excess of bile pigment. As a rule there is not much evidence of foci of hyperplasia in the lobules unless the condition be of long duration, which is unusual, but the livers are usually not reduced in size, nor is fatty infiltration a feature of the condition.

This series of 13 cases comprised seven males and six females, with a mean age of 62. The average weight of the liver was 1,400 g. Two typical cases are given below.

*Case 4131.*—A woman aged 45 suffering for two months from jaundice due to obstruction of the common duct by

carcinoma of the head of the pancreas, which was complete at the time of the post-mortem examination. The liver showed a very marked lobular pattern due to central necrosis with some fibrous replacement and bile staining, but without great increase in the portal fibrous tissue (Plate, Fig. 1). This is not an advanced lesion.

*Case 489.*—A man aged 66. His condition was due to an intrahepatic bile-duct carcinoma causing complete obstruction. The duration of the jaundice was given as nine weeks. The sections (Fig. 2) show a most advanced fibrosis of the portal tracts, which are joined up throughout the liver, whilst the central areas are pigmented and also fibrous. Bile-stained plugs are present in some of the ductules and there is very marked overgrowth of bile canaliculi. The quantity of surviving liver tissue is greatly reduced. Bile necroses were also seen.

### Cardiac Cirrhosis

This occurs as a result of chronic venous congestion of the liver with distension of the sinusoids. The mean age is lower than in biliary or portal cirrhosis owing to the frequency with which the condition results from rheumatic heart disease. It is more common in women than in men. There is usually a long history of congestive failure, with auricular fibrillation. In this series there were 20 cases (6 males and 14 females). The mean age at death was 52, and the average weight of the liver 1,620 g.

The livers tend to be large, more especially in the younger subjects, owing to congestion and often an element of oedema: in the more elderly the process of atrophy becomes more pronounced. Like other forms of cirrhosis it is often worse in the left lobe than in the right. The centrilobular congestion leads to atrophy of the central cells and a condensation and increase in the quantity of the central reticulin, which ultimately becomes collagenous, so that a central scar develops. At the same time there is always some increase in fibrous tissue in the portal tracts, with the appearance of rudimentary bile canaliculi. By slow degrees the portal fibrous tissue stretches out its tentacles to reach the central fibrotic areas, and thus a network of scar tissue of considerable complexity is formed all through the liver. The production of foci of hyperplasia is not much in evidence. In some cases rudimentary bile canaliculi appear in the central as well as in the portal tracts. It seems to me that often these structures are formed by the atrophy and anaplasia of liver-cell columns, or parts of liver-cell columns, and not always by a sprouting of young bile ducts from the portal tracts, as is commonly held. Occasionally some evidence of obstruction to biliary canaliculi may be seen in the form of bile thrombi, supporting the view that the mild jaundice which these patients sometimes show is due to intralobular stagnation of bile. The following are three sample cases.

*Case 620.*—A woman aged 50 dying from congestive failure following chronic hypertension. The liver weighed 2,520 g. and showed a doubtful excess of portal fibrous tissue with some collagenous scarring of the central vein areas of the lobules: a mild change.

*Case 4471.*—A woman aged 22 suffering from severe rheumatic heart disease with mitral and tricuspid stenosis, pericarditis, and auricular fibrillation. The liver weighed 2,300 g. and showed a severe fibrosis of the central areas, which are linked with the portal tracts by continuous sheets of fibrous tissue in which many bile canaliculi are seen: a severe case of long standing (Fig. 3).

*Case 4140.*—A man aged 58, who during eight years had been several times in hospital for congestive failure from myocardiac disease and relative valvular incompetence with auricular fibrillation. The liver showed a remarkable degree of central lobular destruction, so that the only surviving cells were those around the portal veins (Fig. 4). The picture was a striking illustration of "paradoxical lobulation." The areas of atrophy were not as fibrous as in the previous case, the element of congestion being greater, but there was more loss of liver tissue, since the weight of the organ was only 1,010 g.

### Syphilitic Fibrosis

Apart from the congenital form of pericellular cirrhosis seen in congenitally syphilitic infants and which is a characteristic and well-recognized lesion, there is some confusion about the part played by syphilis. Since the arsenotherapy period the matter has been made obscure by the relationship, until recently misunderstood, of jaundice and acute hepatic necrosis in treated syphilitics to the disease itself and to arsenical poisoning. It is now generally agreed that this hepatic affection is due to infection of the patient with the virus of homologous serum jaundice, and that the fibrosis which may develop later is a sequel to a hepatitis and has nothing to do with syphilis.

With this point clear there seems little left to "syphilitic cirrhosis" but the fibrosis which follows tertiary gummatous infiltration. In this series there are several cases in old syphilitics with positive serum tests in whom the livers show irregular coarse scarring, roughly stellate, and radiating from a central focus, which no doubt represents healed tertiary lesions, and which in its highest development gives the classical picture of hepar lobatum.

### Portal Cirrhosis

Turning now to portal cirrhosis, it is my main thesis that there is one picture of portal cirrhosis whether it follows a known hepatitic infection, as it unquestionably may do, or whether it be cryptogenic. In illustrating my contention I propose to draw upon the 80 cases of portal cirrhosis which I have reviewed at post-mortem examinations and to relate the findings in these to those seen in both early and late cases of acute hepatitis. The details of the two series are:

| | Cases | Male | Female | Mean Age | Mean Liver Weight |
|---|---|---|---|---|---|
| Portal cirrhosis | 80 | 51 | 29 | 58·5 | 1,391 g. |
| Fatal hepatitis | 29 | 16 | 13 | 37·0 | 1,250 g. |

Now, with few exceptions the cases of these liver diseases which come into the hands of the pathologist are either those of the acute form, which are fatal after a short illness, or are cases of chronic disease in which death occurs after a long illness and which show advanced cirrhosis. The land in between is to be explored only by the method of biopsy, or through the chance of death from some intercurrent cause, and, though by this means we are able to follow the natural history of the disease in a few cases, this has hardly yet been done on a sufficient scale for our knowledge to be generally applied, as full and accurate information of the pathology of acute hepatitis dates only from about 1939.

I propose to take first the lesion of which we know the earliest stages well—infective hepatitis—which we believe to be an acute virus infection, and to follow it through the different stages of its natural development and then, with this picture in mind, to see to what extent the changes found in cases of cryptogenic cirrhosis fit into a like process of evolution.

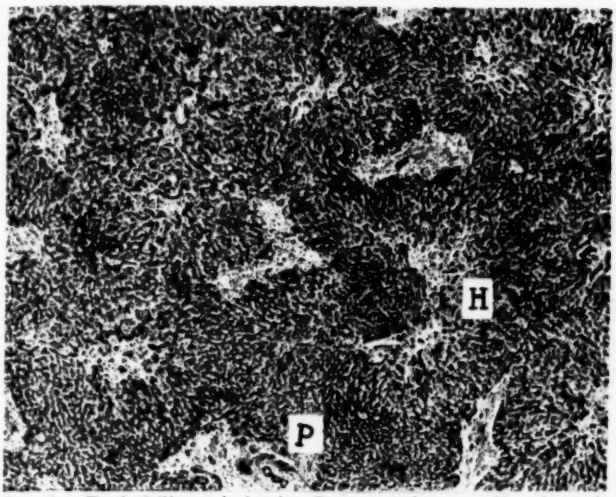


FIG. 1.—Early biliary cirrhosis. P = portal zone; H = hepatic zone. (× 27.)

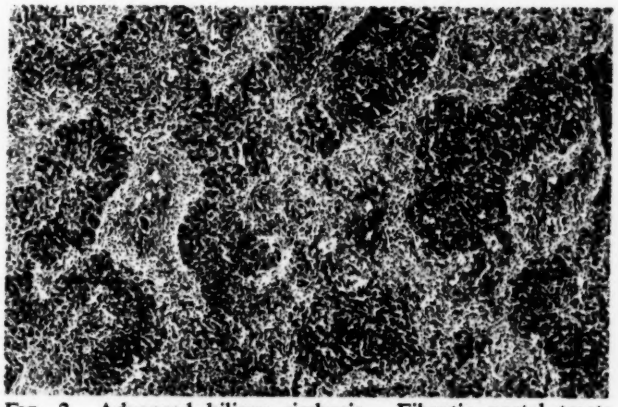

FIG. 2.—Advanced biliary cirrhosis. Fibrotic portal tracts have united. (× 27.)

FIG. 3.—Cardiac cirrhosis. Surviving liver cells in portal zones (arrows). Fibrosis at lobular centres. (× 36.)

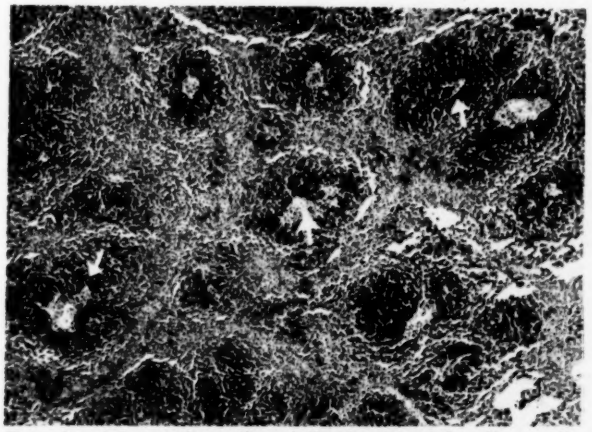

FIG. 4.—Advanced cardiac cirrhosis. Surviving liver cells in portal zones (arrows). Fibrous hepatic-vein tracts have united. (× 21.)

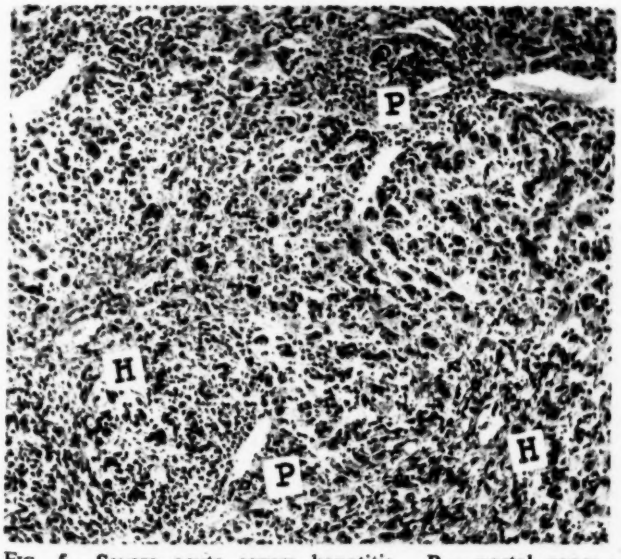


FIG. 5.—Severe acute serum hepatitis. P = portal zones; H = hepatic zones. (× 75.)

FIG. 6.—Severe acute infective hepatitis. (× 127.)

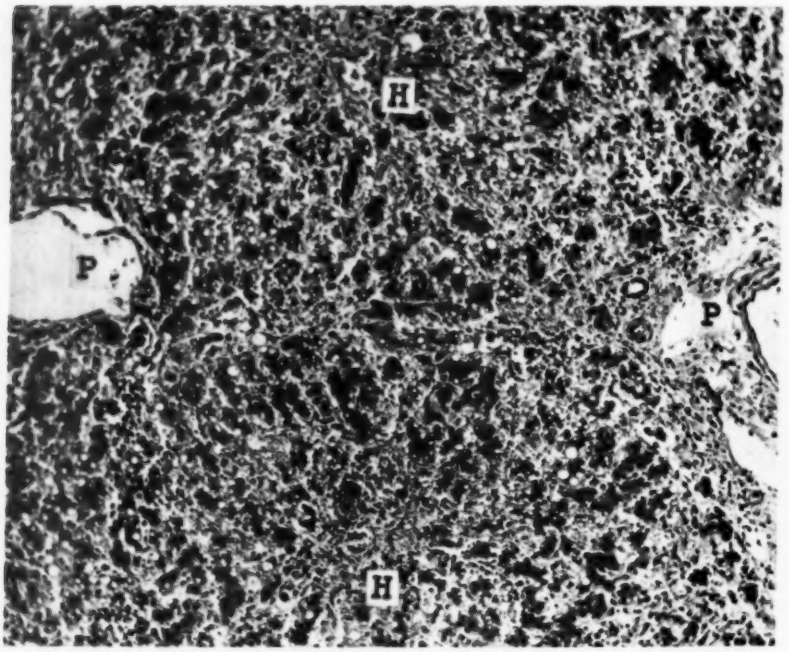


FIG. 7.—Fatal acute hepatitis. Liver lobules recognizable ; necrosis not become confluent. (× 75.)

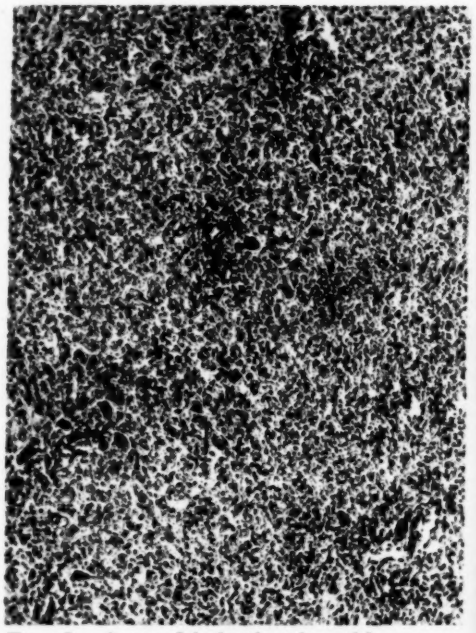

FIG. 8.—Acute fulminating hepatitis ; confluent hepatic necrosis. (× 75.)

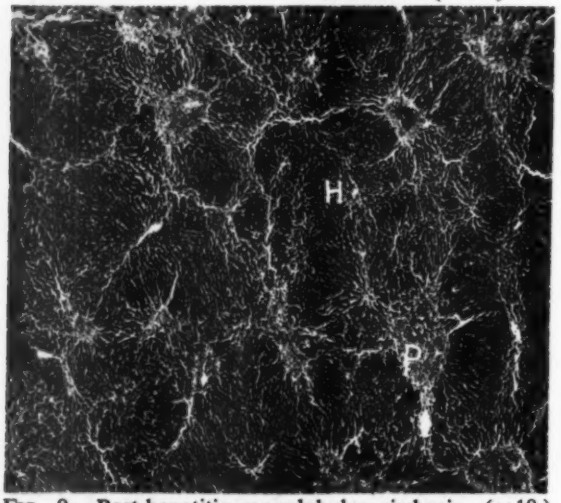


FIG. 9.—Post-hepatitic monolobular cirrhosis. (×18.)

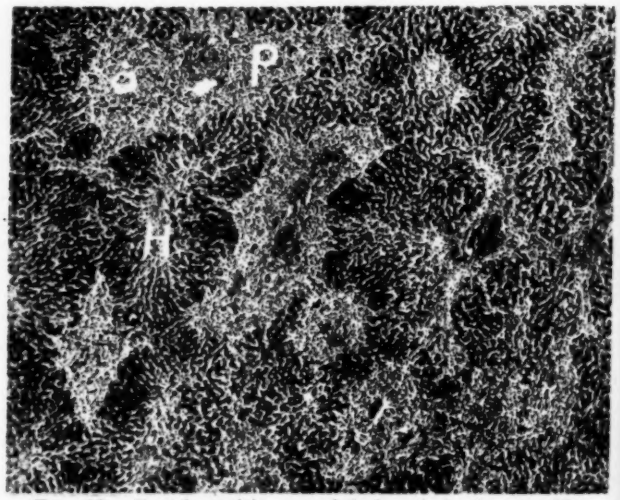


FIG. 10.—Post-hepatitic monolobular cirrhosis. (× 27.)

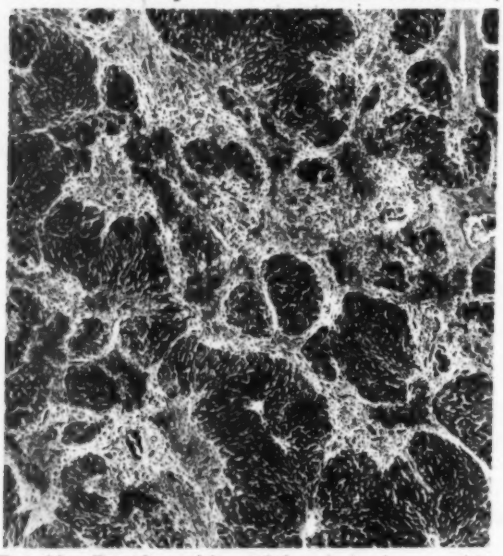

FIG. 11.—Post-hepatitic nodular cirrhosis. (× 18.)

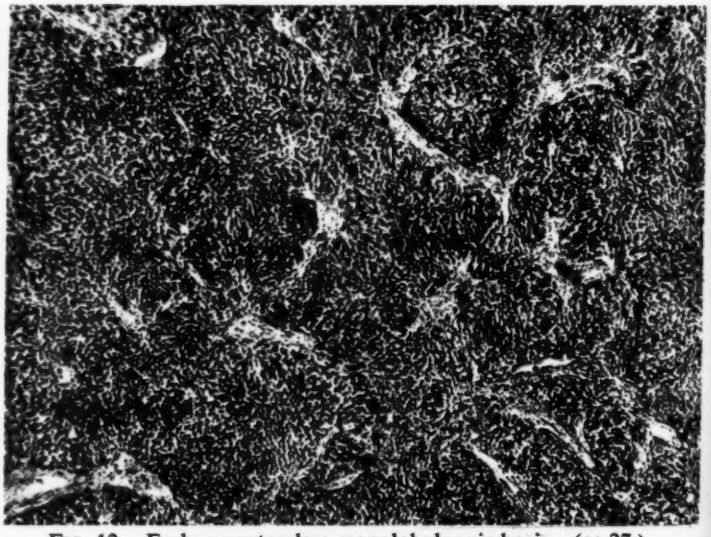

FIG. 12.—Early symptomless monolobular cirrhosis. (× 27.)

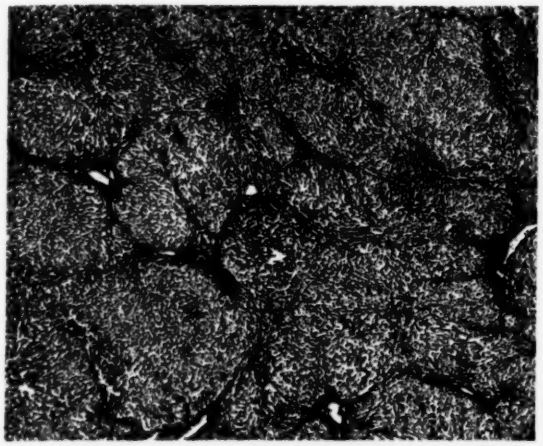

FIG. 13.—More advanced early symptomless cirrhosis. (× 18.)

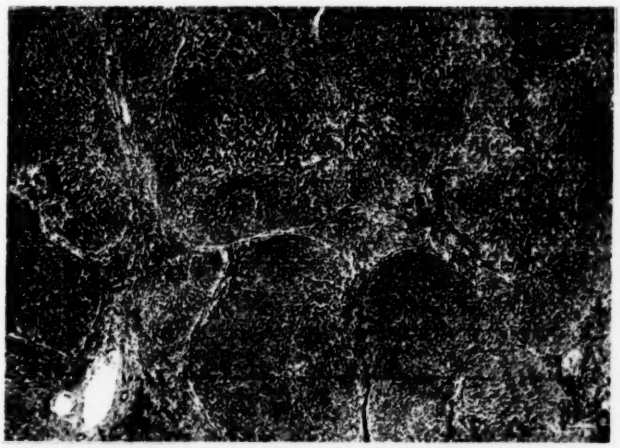

FIG. 14.—Early symptomless multilobular cirrhosis. (× 19.)

FIG. 15.—Nodule of regeneration within a cirrhotic liver. (× 27.)

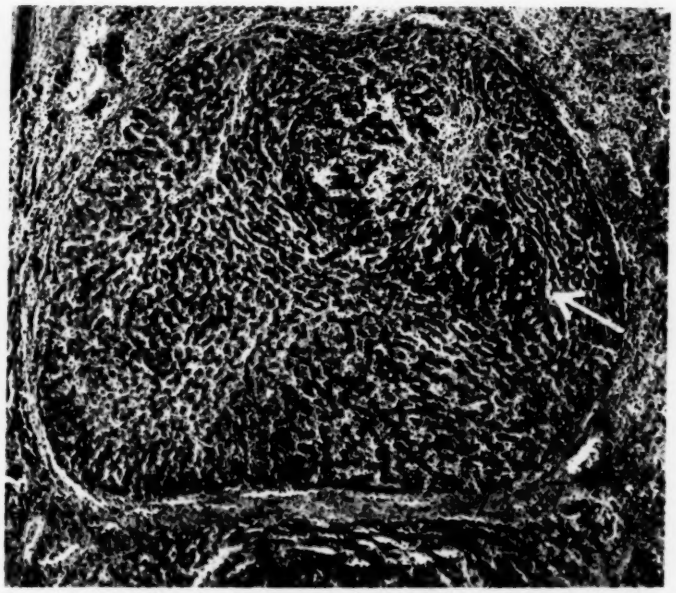

FIG. 16—Nodule of adenomatous hyperplasia in a cirrhotic liver. Arrow shows neoplastic cells. (× 43.)

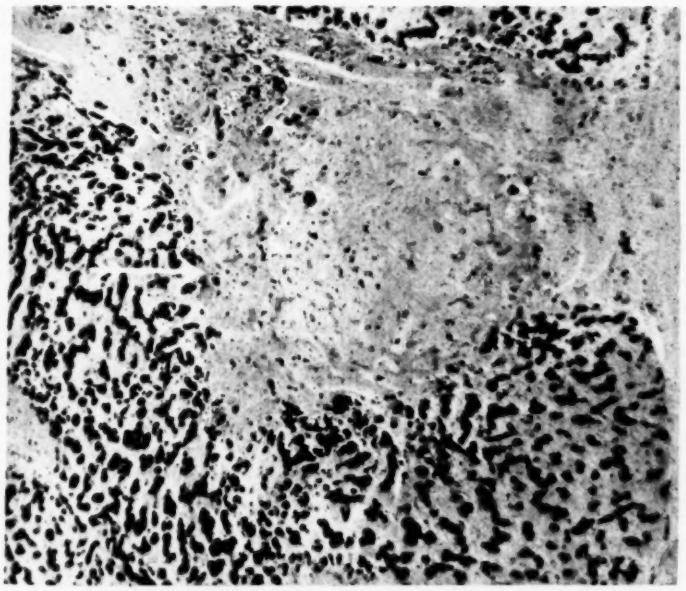

FIG. 17—Nodule of regenerating liver in haemachromatosis. (Pigment absent from young liver cells.) (× 73.)

FIG. 18.—Survival of a hyperplastic nodule growing among older cells, in acute necrosis of a cirrhotic liver. (× 30.)

FIG. 1.—Thin deposits of fibrin on surface of valve. Organization represented by underlying pale zone. Frozen section. (Haemalum. × 185.)

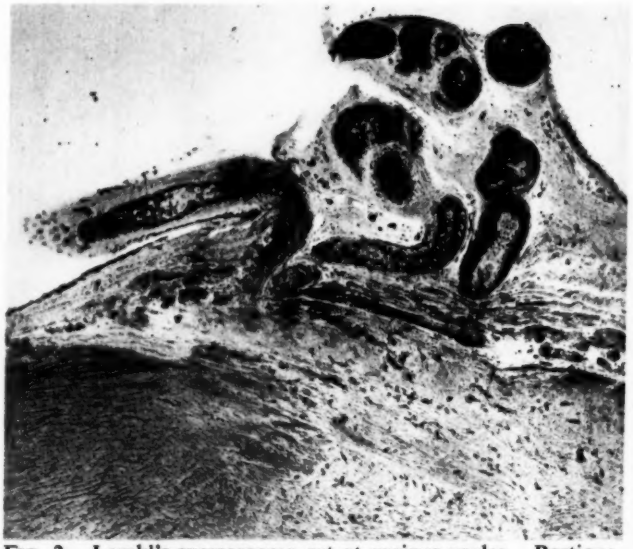

FIG. 2.—Lambl's excrescences cut at various angles. Portions of some are buried beneath surface of valve. Frozen section. (Haemalum. × 44.)

FIG. 3.—A recent fibrin deposit in a commissure causing the two cusps to become adherent. Frozen section. (Haemalum. × 48.)

FIG. 4.—An organized adhesion, partially obliterating angle of commissure between the cusps. Frozen section. (Haemalum. × 48.)

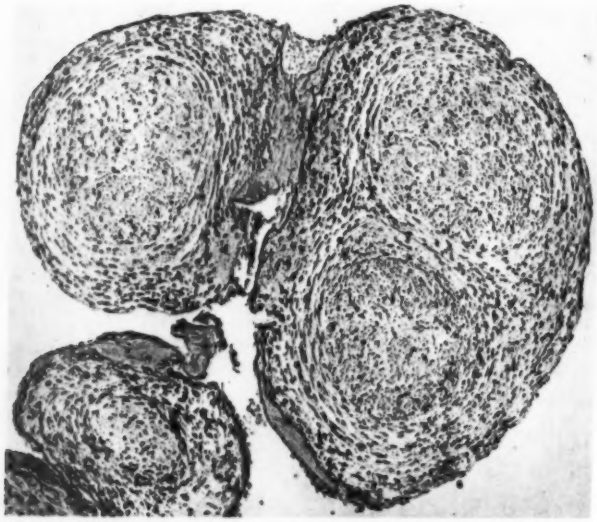

FIG. 5.—From a case of acute rheumatic fever. Chordae tendineae bound together by fibrin deposits in which organization is starting. (Haemalum and eosin. × 82.)

FIG. 6.—Section through a thickened cusp. Chordae tendineae buried in ventricular aspect of cusp. Frozen section. (Haemalum and elastic stain. × 12.)

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### Acute Hepatitis with Recovery

The picture in ordinary acute hepatitis is that of a partial necrosis within each lobule, this being especially severe at the centre, in the zone of the hepatic vein. At the same time there is considerable cellular infiltration of the portal tracts. These features are well shown in the following typical cases:

*Case 42/711.*—Arsenotherapy jaundice of five days' duration. Serum bilirubin, 14.2 mg. Biopsy showed a very severe lesion (Fig. 5). Recovery followed.

*Case 44/309.*—Biopsy of an acute hepatitis (not serum) with 11 days' jaundice and a serum bilirubin of 18 mg. (Fig. 6). A month later the jaundice had gone and the lesion had greatly regressed, though still recognizable; the infiltration of the portal tracts was obvious, with some excess of fibrous tissue.

*Case 44/212.*—Arsenotherapy jaundice of seven days' duration; serum bilirubin, 13 mg. A very severe lesion. This case was followed by consecutive biopsies by Dr. Sherlock until the 60th day, by which time the lobular pattern was fairly well restored and the jaundice had disappeared, though residual lesions were still very obvious in the liver in the form of cellular infiltration and an excess of fibrous tissue in the portal tracts, tending to extend from lobule to lobule.

These are all examples of the severer cases which recover. Most of such cases ultimately achieve complete clinical recovery, though this may be delayed and convalescence be prolonged. The lesion in the liver is apt to persist for some time after the jaundice has disappeared, as can be shown by serial biopsies.

### Fatal Acute Hepatitis

Let us now look at the severer grades of the lesion, seen in fatal cases. Here we usually find an extension and a confluence of the acute lobular lesions—a picture which has long been called "subacute atrophy," while the most severe cases with a fulminating course die with a yet more massive necrosis—the old "acute yellow atrophy." That these are mere gradations in a single process can be illustrated by the following example:

*Case 238/48* (kindly given me by Professor Dorothy Russell).—A girl aged 11 who suffered from homologous serum jaundice following transfusion and died on the seventh day after the appearance of jaundice. There was an exquisite necrosis which was still unilobular (Fig. 7)—a hepatitis hardly more severe than is seen in some of our biopsies from patients who have recovered. I would stress that this was still a lobular necrosis, although ending fatally, as it showed that not all patients who die have the confluent necrosis, which is more commonly seen, in which lobular pattern is lost.

The next case shows the more usual picture, in which the lobular lesions have become confluent, which is the anatomical transition from simple hepatitis to massive necrosis, but does not warrant a special descriptive name.

*Case 2695.*—A man aged 27 suffering from arsenotherapy jaundice of six days' duration. This unfortunate individual died of haemorrhage after hepatic puncture. Both biopsy and necropsy specimens showed a severe lobular hepatitis with the lobule boundaries becoming merged through the total destruction of hepatic cells, and over considerable areas all lobular structure becoming lost.

The final stage in this progression from lobular to a confluent lesion is seen in the following case of fulminating hepatitis.

*Case Ogglesby* (Dr. Beryl Lawrence).—A soldier aged 21 received a transfusion on December 27, 1944. On February 16, 1945, he became ill, developed jaundice, rapidly passed into coma, and died on February 18. The liver showed an acute confluent necrosis with an almost complete destruction of all hepatic cells (Fig. 8).

### Relenting Hepatitis

What sort of changes result if this acute hepatic process relents and heals? As I have said, *restitutio ad integrum* is the usual event, often with a little portal scarring of no consequence, but more severe sequelae can occur. We can, in fact, find a series of healed or healing lesions of progressively increasing gravity, as is shown and illustrated in the following cases:

*Case Cockburn* (Dr. Amies).—A man who had a moderately severe attack of hepatitis, from which he recovered except for marked mental depression. He committed suicide at a convalescent home about seven weeks from the onset of his illness, and four weeks after leaving hospital. The liver showed quite marked parenchymatous changes still present at the centres of the lobules, and some infiltration and undue prominence of the portal tracts.

### Cirrhotic Sequelae of Hepatitis

Many cases which recover completely show some residual fibrosis in the portal tracts which seem to be of no importance, but a certain number show definite fibrotic lesions which have all the characters of a developing cirrhosis.

*Case 3569.*—A woman aged 75, with a long history of gastro-intestinal haemorrhage, possibly purpuric in nature, as the cause was never satisfactorily explained, but with no evidence of portal obstruction. She claimed to have had 82 pints (46.6 litres) of blood transfused over 5¼ years. There were no symptoms of cirrhosis, but a diagnosis of hepatic fibrosis was made in the post-mortem room. The probability of a homologous serum hepatitis at some time is high. There was a fine portal scarring with a tendency to the junction of the fibrous bands (Fig. 9). The picture was very similar to that in early cryptogenic cirrhosis (see Fig. 12).

*Case 3523.*—A man aged 59; a known case of recent homologous serum jaundice which had developed during treatment for syphilis. The hepatitis had subsided and he had no symptoms of cirrhosis, but he died later of bronchopneumonia following radiotherapy for an oral carcinoma. This case showed marked scarring of a more advanced grade (Fig. 10).

If we leave these asymptomatic lesions and turn to cases of hepatitis dying after long delay from hepatic insufficiency, or those still alive who have symptoms of liver disorder, we naturally find a more advanced picture.

I have first to refer to two cases examined only by biopsy.

*Case 42/608.*—A man aged 29 with serum hepatitis. Biopsy on the 120th day, when the serum bilirubin had returned to normal, showed a decided fibrosis with a tendency for the liver parenchyma to be divided into rounded areas by anastomosing fine strands of fibrous tissue. This case is illustrated as Fig. 11 in the article by Dible, McMichael, and Sherlock (1943). A further biopsy two years later showed a similar picture.

*Case A.27174* (Dr. C. V. Harrison).—A case of hepatitis after transfusions, resulting in an enlarged liver 10 months later for which the abdomen was explored and a biopsy taken. The picture was one of coarse multilobular cirrhosis. Five years later the patient was still alive, but jaundiced and with enlarged liver and spleen.

Finally, let us look at the lesion seen at necropsy in delayed fatal hepatitis.

*Case 4370.*—A woman aged 66 who died from an attack of infective hepatitis of four to five weeks' duration. The necrotic cells have now disappeared and the replacing fibrous

tissue bands have become confluent; both single lobules and partially regenerated multilobular nodular areas of liver have survived. This was the condition in the right lobe (Fig. 11); in the left lobe confluent necrosis followed by fibrosis dominated the picture.

### Cryptogenic Cirrhosis

We have thus passed in review a whole gamut of stages from apparently harmless portal scars, through monolobular cirrhosis, up to the condition of nodular hyperplasia, as the results and sequelae of a known earlier acute hepatitis. It remains to ask if we can find analogous changes in insidious cryptogenic portal cirrhosis. To examine the beginnings of this process we must turn to the symptomless cases of cirrhosis which are found at necropsy on patients dying from another cause. Here we can trace a similar evolution from a monolobular lesion.

*Case 310.*—A man aged 60 who died from a renal carcinoma. At necropsy a symptomless cirrhosis was found, with a liver rather above normal weight (1,890 g.) which showed a fine lobular cirrhosis (Fig. 12).

*Case 416.*—A man of 57 who died from carcinoma of the stomach. His cirrhosis was also unsuspected. The liver was of normal weight and showed a more advanced condition than the first (Fig. 13).

*Case 1203.*—A man of 24 who died from acute meningitis. The liver was a little above normal weight. The cirrhosis was symptomless. It showed an advance on both of the previous cases and undoubted evidence of nodularity and multilobular fibrosis (Fig. 14).

The difficulty which always faces us when we see these static-looking quasi-monolobular fibroses is to know whether the condition is really progressive, and therefore the early stage of a Laennec's cirrhosis, or whether it can retrogress; and, secondly, how the vastly different picture of polylobular cirrhosis, with its big complex nodules and thick bands of fibrous tissue, is produced. On the first point we get enlightenment from the experiments of Cameron and Karunaratne (1936), who found that, whilst a certain degree of experimentally produced fibrosis of the liver would retrogress, when this was exceeded the cirrhosis became permanent, even though the immediate exciting cause had ceased to act. They also illustrate in their paper, very clearly, a transition from a fine monolobular type of cirrhosis to one showing the picture of a nodular fibrosis, by the mere continuance of the action of the poison—carbon tetrachloride.

The transition of a monolobular to a multilobular picture in portal cirrhosis is, I believe, a regular process which proceeds as follows. The hyperplastic nodules are often thought to develop from isolated islets of liver cells "cut off" by fibrosis or surviving the process of necrosis. This they may certainly do in the phase of recovery, or reaction, in an acute hepatitis in which the necrosis is confluent. But it is less easy to visualize the transition from a monolobular to a multilobular fibrosis, and, however this may take place, it would seem inherently improbable that small islets of liver once they become surrounded by fibrous tissue should become hyperplastic. If there should be a stimulus to the liver to undergo hyperplasia (for which it has marked capacity) it seems likely that the response will be in those parts of the liver with the best blood supply: in the fibrotic livers we have been discussing this is within the existing lobules, and in livers which have been damaged by acute necrosis within the larger surviving areas rather than in the smaller. This process in chronic cirrhosis can be seen in its beginning in Case 1203, which I have already illustrated (Fig. 14), and can be further observed in the following cases, some of which were asymptomatic and others advanced.

*Case 1826.*—An elderly man, accidentally killed, was found to have a symptomless cirrhosis. The liver was of normal weight and showed a fine unilobular cirrhosis with early hyperplastic nodules.

*Case 4912.*—A man of 67, dying of operation for carcinoma of the rectum, who had a liver of normal weight and a symptomless coarse multilobular cirrhosis—some of the larger nodules of liver tissue showed developing hyperplastic nodules.

A single illustration (Fig. 15) will suffice to show the condition.

*Case 1507.*—An advanced cirrhosis in a man aged 83 dying of coronary thrombosis. The liver weighed only 620 g. The development of nodules is well seen in some of the less affected parenchymatous areas.

I believe that new foci of hyperplasia arise within existing areas of liver which are not yet fibrous. A competition develops between the older liver cells and those of the new hyperplastic area that often seems to result in the pressure atrophy of the former—in which the cells can be seen to be flattened and atrophic in the photographs—and their disappearance, with the development of a peripheral fibrosis and perhaps the formation of two or more nodular areas in the place of one; or perhaps the replacement of the parent nodule in its entirety. When the fibrosis of the liver is as yet not far advanced large nodular areas can be formed if the growth impulse within the new cells exceeds that of the rest of the liver. Evidence in support of this view that the site of election for proliferation is intranodular is given by the following case of cirrhosis with multiple hepatic adenomata.

*Case 2026.*—A man aged 39 who had the symptoms of cirrhosis, which condition was diagnosed. The liver was much enlarged, and at necropsy it was found that in addition to cirrhosis there were numerous multicentric hepatic adenomata widespread through the liver. The condition, though neoplastic, has a certain analogy with that of nodular development of liver cells which I have just been discussing. The growth of the neoplastic hepatic cells, which can be recognized easily by their different appearance, is clearly from a portal tract within one of the larger areas of nodular hyperplasia (Fig. 16). It is not unreasonable to suppose that this indicates a site most favourable for new proliferation.

Finally, a very convincing piece of evidence is to be found in some of the hyperplastic nodules in the cirrhotic liver of haemochromatosis. Here the older liver cells are heavily impregnated with iron pigment, but newly formed foci have only had time to accumulate little pigment, and by this fact can be readily recognized. Nodules of hyperplasia of different ages can be distinguished by this fact, and it is clearly seen that the new ones arise within the larger and older nodules (Fig. 17).

It is to be remembered that the progress of cirrhosis is very far from being continuous, but proceeds by fits and starts, and that episodes of pyrexia, and especially of jaundice, indicate an extension of the necrosis which affects the cells unevenly, producing focal areas of liver-cell death in which fibrosis follows. This inequality in resistance of different hepatic cells is illustrated in an extreme degree by the following case:

*Case 42/822.*—A woman aged 39 had suffered from painless jaundice for six months. An exploratory laparotomy was done and a search made for an obstruction, which was not found. The patient failed to rally from the operation and died the next day. At necropsy no obstruction was discovered, but a cirrhotic liver was present which showed

the most marked extensive patchy necroses of the nodules, the necrotic cells being selectively stained with bile. A point which I wish to stress, apart from this acute necrosis following a severe operation, is the way in which some areas of recent nodular hyperplasia, developing within existing nodules in the way I have mentioned, have escaped the necrosis (Fig. 18)—indicating their functional independence of the remainder of the nodule, which it seems fair to assume is due to an independent and better blood supply.

### Conclusion

I conclude therefore that the final picture of polylobular cirrhosis is the end-result of a lesion which in the beginning is monolobular. Where the initial lesion is an acute hepatitis healing is often complete: in severer cases of this disease, however, healing may take place without the immediate destruction of the lobular pattern, but nevertheless leave a lesion which continues to progress and ultimately, by a process of nodular hyperplasia, develops into a coarse fibrosis, in the way I have indicated. Where the acute lesion is of sufficient severity for the necrosis to become confluent during the initial phase of the disease the earlier appearance of a polylobular fibrosis is to be anticipated. Likewise, where the cirrhosis is cryptogenic (and it is possible that many of these cases may originate as a disguised hepatitis) a similar symptomless monolobular lesion occurs, which may follow the same evolution and in the end produce an indistinguishable lesion.

### Summary

Largely as a result of experimental observations on animals, in particular the rat, a new conception of the pathology of liver degeneration, involving fatty change and necrosis and leading ultimately to fibrosis, has been developed. It seems necessary to examine this matter in the light of human pathological experience and of the more recent work upon hepatitis and its sequelae. The conception that fatty infiltration of the liver is a precursor of the common form of cryptogenic portal cirrhosis finds little or no support from such evidence as has been adduced in this study.. From this it follows that any classification of human cirrhoses according to such a view of their aetiology is untenable. Fibrosis of the liver of varying degrees may be produced by a variety of agencies, and, as has long been admitted by pathologists, the two chief events which lead to portal cirrhosis, which is no more than a late stage of progressive portal fibrosis, are a previous acute or subacute hepatitis, which in the beginning may be either monolobular or confluent, and a cryptogenic slowly progressive disease which may or may not be due to diet, but which does not appear to be preceded either by severe fatty infiltration or by extensive acute necrosis. The end-results of either process, though these may differ in the rate at which they evolve, are similar and are due to progressive destruction of liver cells associated with attempts at their regeneration. This occurring within the framework of fibrous scar tissue produces the nodular appearance so characteristic of many cirrhotic livers.

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# CORTISONE IN THE TREATMENT OF TOXAEMIA OF PREGNANCY*

## A STUDY OF EIGHT CASES

BY

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A continuous supply of cortisone, prepared by Messrs. Merck and Co. under the proprietary name of "cortone," has been given since last May to the Medical Research Council of Ireland through one of us (H. M.). For a variety of reasons it seemed that this hormone might be useful in the treatment of the toxaemia of pregnancy, and we now report the results of treating eight cases with it.

Toxaemia of pregnancy may perhaps in part be explained on the hypothesis that it is a manifestation of Selye's general adaptation syndrome, the stress being some unknown (possibly biochemical) factor related to pregnancy. Further, the somewhat conflicting evidence on the role of the adrenals in this condition might be held to justify a trial of cortisone. Fauvet (1936) observed that the adrenals were below normal size in fatal cases of eclampsia. Fauvet and Munzer (1937) also reported a low concentration of pituitary corticotrophic hormone in eclampsia. On the other hand there is also considerable evidence that the adrenals are hyperactive in normal later pregnancy (Venning, 1946). Again, Tobian (1949) observed a high urinary level of mineral-controlling corticoids in pregnant women with oedema due to toxaemia, while Davis and Hulit (1949) found a low eosinophil count in two cases of eclampsia.

The observations of Tobian are of particular interest, as there is a clinical resemblance between toxaemia of pregnancy and intoxication with deoxycortone (D.C.A.); both conditions may exhibit oedema, hypertension, and albuminuria with a normal blood urea (Ferrebee *et al.*, 1939; Altschule and Zamcheck, 1942). Furthermore, both conditions are improved by a low sodium intake

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(Strauss, 1940; Perera and Blood, 1947; Knowlton *et al.*, 1947; Selye *et al.*, 1949) and in both there may be exacerbations if sodium intake is excessive (Selye and Stone, 1943; Strauss, 1940). If pregnancy toxaemia is at least in part due to excessive secretion of corticoids controlling mineral metabolism, it is possible that a relative deficiency of the glucocorticoids may be a contributing factor; indeed, Selye (1949) has postulated a limited degree of antagonism in the body between these two types of hormone.

Nevertheless, it was with a certain amount of reservation that we ventured to give cortisone (in some respects a salt-retaining hormone) to toxaemic patients, knowing that any further water–salt retention might result in convulsions. On full consideration, however, this possibility seemed unlikely, as Farnsworth (1950) had already reported hopeful results with adrenocorticotrophic hormone (A.C.T.H.) in two cases of acute nephritis. In the discussions which followed Farnsworth's report other workers recorded beneficial results in nephrosis; in some such cases a remarkable diuresis appeared after a few days and continued long after treatment had been stopped. Keith (1950) tried cortisone on nephritic patients with oedema; in the first few days there was a considerable increase of water retention and proteinuria; after a week a diuresis started and the albuminuria diminished, although the blood urea increased owing to a temporarily increased metabolism. Nephritic patients without oedema responded poorly, as indicated by a rise in blood urea and a fall in renal function.

As the literature contained no reports on the use of cortisone in toxaemia of pregnancy it was decided to try it in carefully chosen cases. After we had treated four cases a paper appeared by Tew and McAlpine (1950) which described a case of eclampsia treated post partum with cortisone for three days in addition to routine treatment.

The preparation of cortisone used in all our cases was a microcrystalline suspension of cortisone acetate, each millilitre of which contained 25 mg. of cortisone. It was given throughout by intramuscular injection. All cases received the routine general treatment for toxaemia —salt restriction, complete rest in bed in a darkened room, with protection from outside noise and other stimuli, and such sedatives as were required to ensure sleep and freedom from restlessness, anxiety, or pain. Once cortisone treatment was started, however, other drugs were used only to such a degree as seemed to be demanded for the safety of mother and infant.

In each case the principal clinical features have been recorded on charts. Figs. 1–8 give details of the daily fluid intake and urinary output, body weight, blood pressure, the presence and degree of albuminuria, body oedema, ascites, and the daily dosage of cortisone in each case. In the Tables are recorded the results of the eosinophil counts and the various biochemical investigations.

### Case 1 (see Fig. 1 and Table I)

The patient was a primigravida, aged 23, at 35 weeks' gestation. There was no relevant past history, and the pregnancy had progressed normally until one week before admission, when the patient had developed oedema of her feet, and headaches. On admission there was marked generalized oedema. The blood pressure was 180/115, and the urine contained 4+ albumin, a small number of erythrocytes, and hyaline casts. She had a slight headache, but no eye symptoms and no retinal changes. The blood urea was 12 mg. per 100 ml. There was no pulmonary or cardiac lesion, and the electrocardiogram was normal. The foetal heart was heard.

During the first 13 days she was treated with morphine, phenobarbitone, paraldehyde, and intravenous magnesium sulphate. For the first 11 days she improved, but on the 12th day her clinical condition began to deteriorate, and on the next day she complained of headache. Treatment with cortisone was begun that evening, the 13th day after admission. On the 14th day there was some clinical improvement, and by the 17th day the clinical improvement was striking, with simultaneous but less obvious improvement in oedema, albuminuria, and blood pressure. The patient remained in very good condition until the 26th day, when it was decided to stop the hormone gradually. There was no significant change in her condition until the 29th day (at 50 mg. of cortisone), when the headache reappeared and the oedema increased. On the next day there was a further increase in the oedema, and the cortisone dose was increased to 150 mg. daily, this dose being continued until the puerperium. The patient improved generally during the next

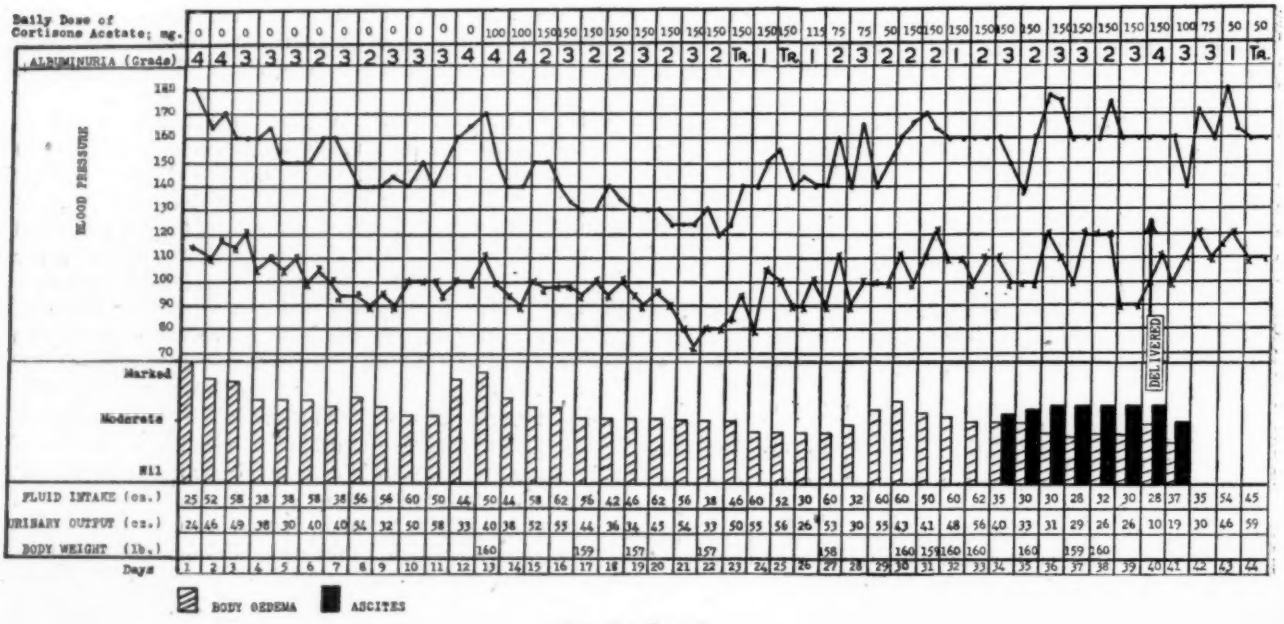


FIG. 1.—Case 1.

TABLE I.—*Results of Biochemical Investigations and Eosinophil Counts on Cases 1, 2, 3, and 4*

| | Case 1 | | | | Case 2 | | | | Case 3 | | | | Case 4 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case Delivered: | 28th Day on Cortisone | | | | 5th Day on Cortisone | | | | 4th Day after Cortisone | | | | 8th Day on Cortisone | | | |
| Days on Cortisone: | 1 | 18 | 28 | 32 | 1 | 6 | 8 | 12 | 1 | 8 | 12 | +7 | 1 | 4 | 12 | +2 |
| Serum sodium (mg./100 ml.) | | | | 332 | | | | | | | | | | | | |
| Serum potassium (mg./100 ml.) | | | | 22·0 | 17·4 | | | | 20·2 | | | | 19·2 | | | |
| Serum calcium (mg./100 ml.) | | 9·6 | | 9·2 | 11·2 | | | | 10·8 | | | 9·6 | 10·8 | | | 7·1 |
| Plasma chloride (mg./100 ml.) | | 660 | | 500 | 620 | | | 630 | 600 | | | 550 | 620 | | | 590 |
| Plasma phosphorus (mg./100 ml.) | | 5·1 | | | 3·9 | | | 4·9 | 4·2 | | | 5·4 | 4·8 | | | 4·5 |
| Plasma carbon dioxide (ml./100 ml.) | | | | 57·0 | 40·1 | | | 53·5 | 38·0 | | | 57·3 | | | | 43·4 |
| Serum uric acid (mg./100 ml.) | 7·6 | 5·7 | | 4·3 | 7·6 | | 5·3 | 4·3 | | 3·5 | 3·8 | | 7·6 | | 4·9 | 4·9 |
| Blood sugar: | | | | | | | | | | | | | | | | |
| Fasting (mg./100 ml.) | | | | | | 115 | | | | 91 | | | | 62 | 105 | |
| 1 hr. after glucose (mg./100 ml.) | | | | | | 190 | | | | 120 | | | | | | |
| 2 hr. after glucose (mg./100 ml.) | | | | | | 140 | | | | 125 | | | | | | |
| Urine 17-ketosteroids (mg. per 24 hr.) | 8·8 | 6·8 | | 4·3 | 6·5 | 7·0 | 2·5 | | 5·3 | | | | | 1·8 | 4·6 | |
| Eosinophil count (per c.mm.) | 150 | 64 | 16 | | 155 | 128 | 128 | | 255 | 32 | 8 | | 0 | 32 | 48 | |

few days, but ascites became evident on the 34th day and it was more marked two days later, when it was accompanied by a further reduction in the oedema.

Labour began spontaneously on the 40th day, and during it there was an exacerbation of all the symptoms of pre-eclampsia. The blood pressure and oedema increased. The urine contained 4+ albumin, fairly numerous hyaline and granular casts, and a few erythrocytes. She had severe headache and blurring of vision. She was treated with intramuscular morphine, paraldehyde, and pethidine, and intravenous 50% glucose and magnesium sulphate. Just at the end of the first stage of labour, which lasted for 20 hours, there was a single convulsion. Forceps delivery was performed immediately under thiopentone anaesthesia. The infant was normal—6 lb. 14 oz. (2.8 kg.)—was breast-fed, and progressed satisfactorily.

The cortisone was gradually reduced, the final dose of 50 mg. being given on the fourth day after delivery. The ascites and oedema had disappeared by the third day. The puerperium was uneventful, the patient being allowed up on the 10th day and home on the 16th day. The urine was free from albumin on the eighth day, and the blood pressure on discharge from hospital was 130/100.

### Case 2 (see Fig. 2 and Table I)

The patient was a primigravida, aged 27, at 40 weeks' gestation. There was no relevant past history. There had been a gradual onset of oedema during the six weeks before admission, the oedema becoming more marked during the last 10 days. There had been intermittent headaches, which had become worse during the past week, and there had also been blurring of vision for the last 48 hours. On admission the patient had gross generalized oedema; the blood pressure was 160/110, and the urine contained 4+ albumin, a few erythrocytes, and a small number of hyaline casts. She complained of severe headache and blurring of vision, but no retinal changes were observed. Her heart and lungs were normal, and the foetal heart was heard.

Routine treatment was started with paraldehyde, morphine, and intravenous magnesium sulphate, but little change was noted at the end of 48 hours; the urinary output, however, remained satisfactory. As no improvement had occurred there was a definite indication for terminating the pregnancy, but it was decided to try treatment with cortisone, starting on the third day after admission. Clinical improvement was apparent on the fourth day, and by the fifth day oedema was much less, there was no headache, sight was normal, and the patient stated that she had not felt so well for weeks. There was a suspicion of some ascites. Next day the patient showed a further remarkable clinical improvement, and she was very bright and talkative in spite of the increased blood pressure. Oedema was much less, although ascites was now marked. Labour began spontaneously at 5 p.m. During the first stage of labour her blood pressure was

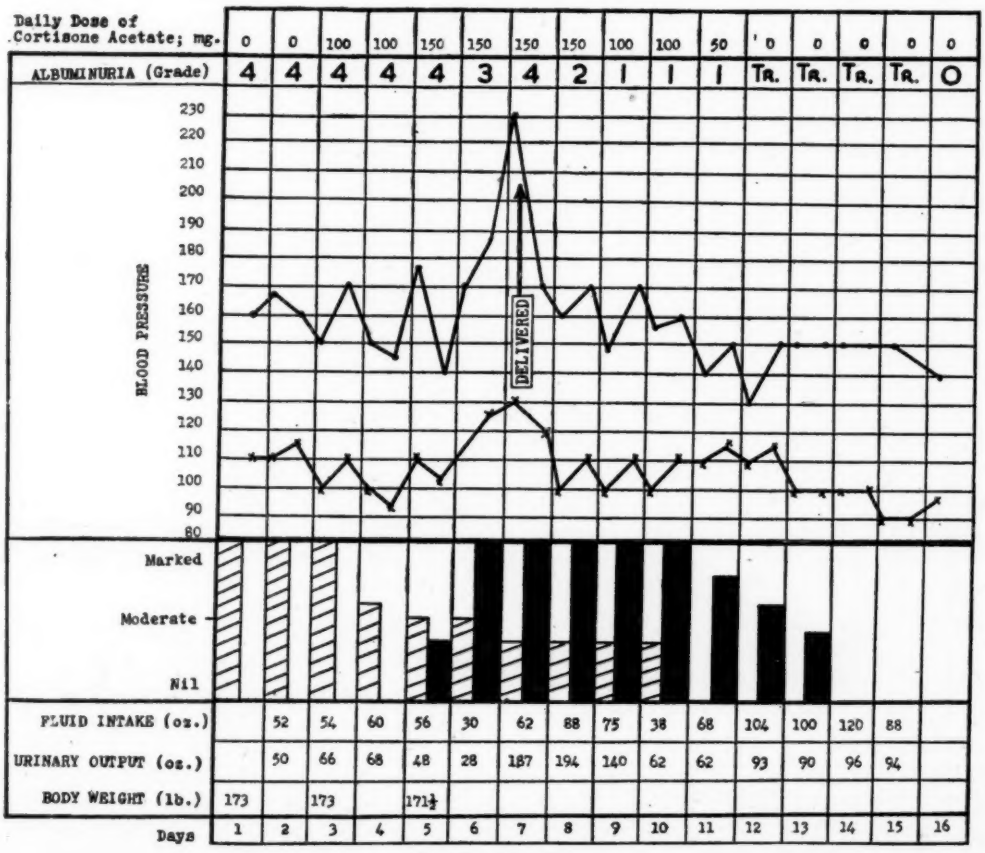


FIG. 2.—Case 2.

230/130, and the albumin was 4+ in her urine, but she had no headache or other complaints. When she had been 25 minutes in the second stage, delivery was effected with forceps. The placenta was retained and was removed manually after one and a half hours. The infant was normal—6 lb. 8 oz. (2.9 kg.)—was breast-fed, and progressed satisfactorily. The mother's progress in the puerperium was also satisfactory (see Fig. 2).

### Case 3 (see Fig. 3 and Table I)

A 3-para aged 42, at 26 weeks' gestation, had no relevant past history. At her first antenatal visit, when 12 weeks pregnant, she was found to have a raised blood pressure (165/110) and cardiac enlargement. Oedema had appeared when she was 20 weeks pregnant, and since then it had become gradually worse in spite of treatment at home for the last four weeks. She complained of having had headaches and giddiness for two weeks. On admission there was generalized oedema and photophobia. The blood pressure was 170/120, the urine contained 4+ albumin, but there were no retinal changes. Microscopical examination of the urine revealed a few erythrocytes and numerous granular casts. There was a mitral systolic murmur which was not propagated. The electrocardiogram was normal, and the foetal heart was heard. For the first 10 days treatment consisted in absolute rest in bed with restriction of fluid and salt, and sedation with phenobarbitone, 1 gr. (65 mg.) thrice daily, and "seconal," ½ gr. (32 mg.) each night; morphine and intravenous magnesium sulphate had each to be given once. This treatment produced little improvement in the oedema, but the headaches were not so severe. The urinary output was satisfactory, and the urinary analysis showed no change. She still had photophobia, and her blood pressure remained elevated. The blood urea was 25 mg. per 100 ml.

Treatment with cortisone, 150 mg. daily intramuscularly, was started on the 11th day after admission, and by the 14th day she felt much improved, her headache had disappeared, she had no difficulty in looking at the light, and she required less sedation. From the 15th to the 19th day there was great improvement in her general condition; the albuminuria and the oedema also improved, but to a lesser degree; and her weight on the 18th day was 4½ lb. (2 kg.) less than at the beginning of cortisone treatment. From the 20th to the 24th day the patient's condition deteriorated; there was headache, a diminishing urinary output, increasing oedema, the appearance of ascites, and a gain in weight. The dose of cortisone was reduced, and stopped altogether after the 24th day, but this had no effect on the progressive increase in severity of symptoms. Twenty-four hours after the cortisone was discontinued the oedema became gross and headache was intense; the pregnancy was now 31 weeks, and labour was induced on the following day by insertion of bougies.

After nine hours in labour the patient had a breech delivery of a premature live infant—2 lb. 3 oz. (1 kg.)—which survived for five days only. During labour the blood pressure rose to 170/110, and the albumin in the urine was 4+. After delivery the patient had a moderately severe post-partum haemorrhage and collapsed, but she responded slowly to blood transfusion, oxygen, etc.; during the remainder of the day she complained of headache. On the first day of the puerperium the oedema was less marked, and there was no oedema on the fifth day; on the seventh day the ascites had disappeared. The albuminuria was still 2+, with a few erythrocytes and fairly numerous granular casts, when she was discharged three weeks after delivery. Her blood pressure had by then fallen to 160/110.

### Case 4 (see Fig. 4 and Table I)

A primigravida aged 24, at 31 weeks' gestation, had a history of intermittent headache and swelling of the feet for five years. This patient had had no antenatal care. Six weeks before admission she developed oedema of her feet and headaches, and remained in bed for a month at home. On admission her face was cyanosed and blotchy, she had gross generalized oedema, a fast pulse of poor volume, and a blood pressure of 230/135. She had intense headache, her vision was very poor, and retinal examination showed small bilateral haemorrhages and blurring of the disks. There was no demonstrable lesion in her heart or lungs, but the rapid weak pulse suggested early cardiac failure. The foetal heart was heard. She was treated with morphine, paraldehyde, intravenous 50% glucose, and intravenous magnesium sulphate; after 18 hours she showed no improvement. Her blood pressure was now 250/130 and the urinary output was 5 oz. (142 ml.). Cortisone treatment was begun 18 hours after admission. By the end of the third day there was great improvement. Vision was much clearer and she could distinguish her husband at once, the

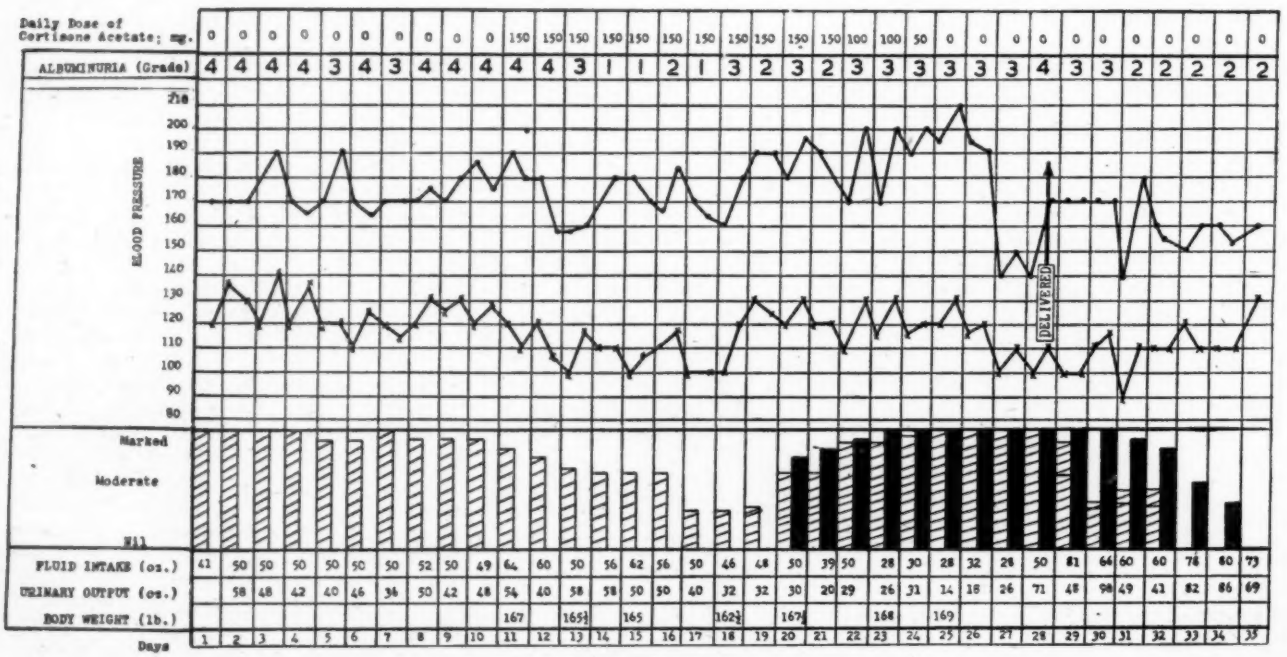


FIG. 3.—Case 3.

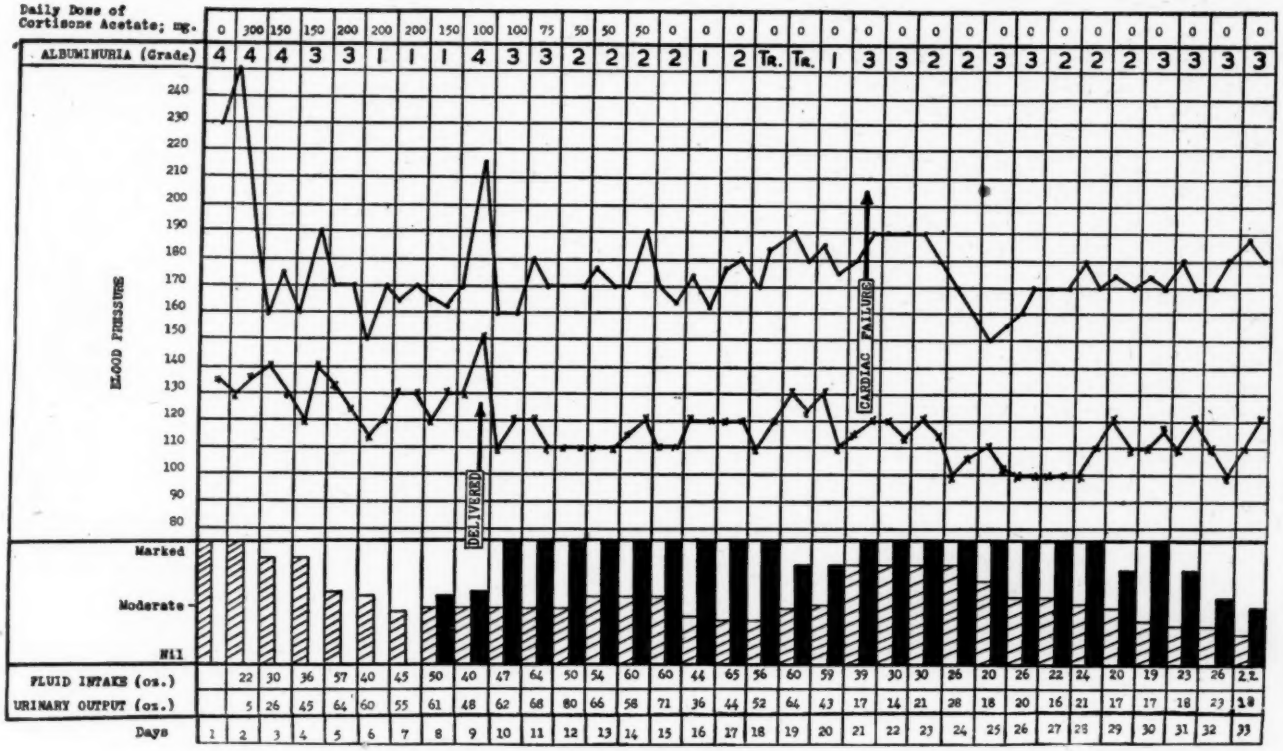


FIG. 4.—Case 4.

headache had disappeared, the blood pressure had decreased, and the optic disks were now more sharply defined. Since admission she had required a special nurse; it was now decided that this was unnecessary.

On the eighth day she felt so well that she suggested getting up, and she had not required any sedative for three nights; ascites became evident, and the dose of cortisone was reduced. On the ninth day the membranes ruptured spontaneously, and the patient had a rapid labour during which the blood pressure rose to 210/150 and the albumin in the urine was again 4+. Pethidine, 100 mg., was given intramuscularly. The baby—3 lb. 3 oz. (1.4 kg.)—was delivered by forceps, but died on the 14th day after birth, post-mortem examination showing an intracranial haemorrhage. After delivery the mother's pulse became rapid and feeble, and her blood pressure fell to 95/60, but she responded to blood transfusion, intravenous dextran, and "methedrine."

The cortisone was gradually reduced, and the final dose was given on the 14th day. On the 12th day she complained of dimness of vision, but her sight gradually improved during the next week. On the 20th day the pulse rate rose to 120, and oedema of her hands and feet increased. Next day she had left ventricular failure with gallop-rhythm and pulmonary oedema, with increased ascites and the reappearance of generalized oedema, a pulse rate of 160, and a fall in the urinary output to 14 oz. (400 ml.); the E.C.G. showed an inverted T wave in Leads I and II. There were numerous red blood cell casts in the urine, and the albumin increased to 3+. The blood urea was 30 mg. per 100 ml. She made slow response to treatment with morphine, continuous oxygen, and digoxin during the next week. Three weeks later this patient was admitted to the Mater Misericordiae Hospital suffering from congestive heart failure. At that time she was dyspnoeic on exertion; her blood pressure was 180/124. The heart was considerably enlarged to the left; gallop-rhythm and a mitral systolic murmur were observed. There were signs of congestion at the pulmonary bases, some oedema of the legs and lumbar cushion, slight hepatomegaly, and possibly slight ascites. Blood examination showed 50% haemoglobin and 2,890,000 erythrocytes per c.mm. A catheter specimen of urine showed albumin 2+, no casts, numerous leucocytes, no erythrocytes, and numerous Gram-negative coliform bacilli. Blood urea was 86 mg. per 100 ml. An E.C.G. showed an inverted T wave in Leads I, II, and III, but Lead IVF was normal and there were no other abnormal features. Notwithstanding vigorous treatment, which did not include cortisone, she died on the 16th day after admission.

### Post-mortem Findings

Post-mortem examination was carried out by Dr. Maurice Hickey 12 hours after death. The body was that of a poorly nourished young woman. Moderate oedema of both lower limbs was present. Approximately 200 ml. of clear straw-coloured fluid was present in each pleural cavity and 50 ml. in the pericardial cavity. The lungs showed moderate venous congestion of both lower lobes. The heart weighed 370 g.; a concentric hypertrophy of the left ventricle was present; the anterior wall of this ventricle measured 1.5 cm., and the posterior wall 1.4 cm. in thickness at a point 5 cm. below the aortic valve. There was moderate atheroma of the coronary arteries. No valvular abnormalities were detected.

The liver weighed 1,500 g. Its surface was smooth and presented a slightly mottled appearance, due to chronic venous congestion. Histological examination showed evidence of slight venous congestion. This was most marked in the left lobe.

The right adrenal gland weighed 3.78 g. and the left adrenal 3.8 g. A small extravasation of blood was present in the tissues posterior to the right adrenal. Histological examination showed venous congestion of both adrenals. This was most pronounced in the medulla and in the inner half of the cortex. In these areas the capillaries were distended with blood and numerous small extravasations of red cells were present. A layer of cells was observed in the cortex of both glands, the cytoplasm of which stained darkly with eosin; this was in contrast to the other cortical cells, in which the cytoplasm stained much less intensely and had a foamy appearance. This layer occupied approximately the outer third of the zona fasciculata. When stained by the ponceau-fuchsin method of Vines the cytoplasm gave a fuchsinophilic reaction. A small area

of necrosis, approximately 2 mm. in diameter, was noted near the mid-point of the renal border of the left adrenal. This necrotic area was in intimate contact with infected renal tissue. No similar necrosed areas were found elsewhere in either adrenal.

The right kidney weighed 135 g. and the left kidney 128 g. A widespread and severe pyelonephritis was present throughout both kidneys. This condition had resulted in the formation of small abscesses in many areas. In the abscesses and in many of the tubules large clumps of Gram-negative bacilli were present. In areas where the inflammatory process was less severe there was evidence of a very marked arteriolar sclerosis. Extreme intimal thickening of the arterioles was present. Necrosis of the afferent arteriole and of some capillary loops in a number of glomeruli was observed. Degenerative changes in the tubular epithelium, especially in the proximal convoluted tubules, were widespread, and varied from simple cloudy swelling of the cells to complete denudation of the epithelial wall.

All other organs examined appeared normal.

### Case 5 (see Fig. 5 and Table II)

The patient, a primigravida aged 24, at 36 weeks' gestation, had no relevant past history. During the week before admission to hospital she had intermittent headaches, but up to this time the pregnancy had progressed normally. Four hours before admission she complained of a severe headache, blurring of vision, and "spots" before her eyes. The blood pressure was then 200/100, and this was the first time that a rise in blood pressure had been detected.

On admission she had only a slight headache, the blood pressure was 150/110, the urine contained 2+ albumin, and there was no oedema. Her heart and lungs were normal, and the foetal heart was heard. There was very little change in her condition the next morning, but the urinary output for the first 12 hours was only 7 oz. (200 ml.), while the fluid intake was 25 oz. (710 ml.). Twenty-four hours after admission she had an acute onset of a very severe headache with dimness of vision; she was sitting up in bed at the time, and while the nurse was getting her to lie down she became unconscious and had a convulsion lasting three minutes; she regained consciousness within five minutes. Intravenous thiopentone was given. There was no change in the blood pressure reading, 150/100, but the albumin in her urine had increased to 3+. During the next 15 hours she was treated with morphine, paraldehyde, and intravenous magnesium sulphate. In spite of heavy sedation she was extremely restless. Ophthalmoscopic examination showed that there was blurring of the right disk. Thirty-eight hours after admission to hospital, and 16 hours after the convulsion, treatment with cortisone was begun. On the fourth day after admission the patient looked well and said she felt better. The dose of cortisone was gradually reduced, and she remained very well until the 11th day, when her condition appeared to have deteriorated, although she did not

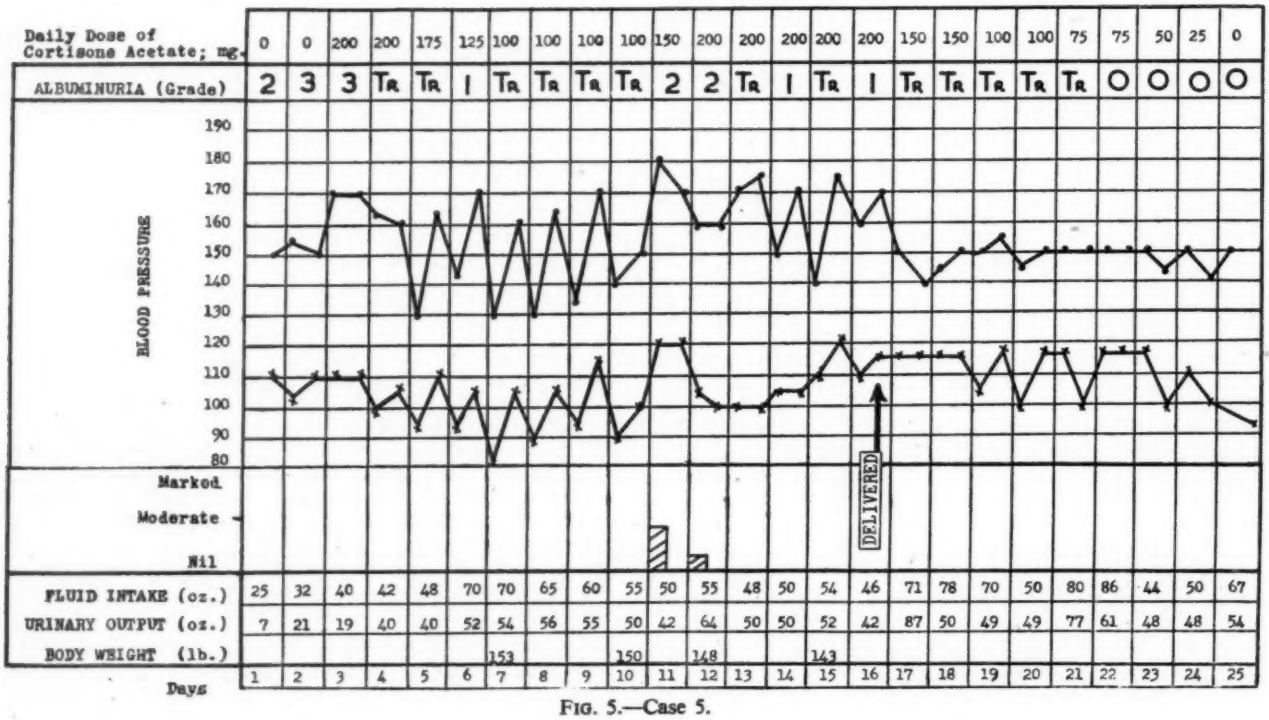


FIG. 5.—Case 5.

TABLE II.—*Results of Biochemical Investigations and Eosinophil Counts on Cases 5, 6, 7, and 8*

| | Case 5 | | | | Case 6 | | | Case 7 | | | | Case 8 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case Delivered: | 14th Day on Cortisone | | | | 8th Day on Cortisone | | | 20th Day on Cortisone | | | | 15th Day on Cortisone | | | |
| Days on Cortisone: | 1 | 8 | 12 | 18 | 1 | 8 | 11 | 1 | 4 | 11 | 22 | 1 | 11 | 18 | 30 |
| Serum sodium (mg./100 ml.) | 327 | 335 | | 335 | 300 | 309 | 310 | 309 | | 312 | 306 | 296 | 291 | 309 | 288 |
| Serum potassium (mg./100 ml.) | 13·3 | 20·0 | | 16·0 | 17·0 | 18·8 | 26·6 | 17·0 | | 17·2 | 20·2 | 15·8 | 15·4 | 19·7 | |
| Plasma chloride (mg./100 ml.) | 597 | | | 550 | 597 | 609 | 620 | 597 | | 597 | 597 | 585 | 585 | 555 | 597 |
| Serum uric acid (mg./100 ml.) | 6·7 | 4·2 | | 7·3 | 4·7 | | 5·0 | 6·1 | 8·0 | 7·2 | 8·2 | 8·8 | 5·9 | | 4·2 |
| Serum protein: | | | | | | | | | | | | | | | |
| Total (g.%) | 5·6 | 5·6 | | 4·5 | 5·6 | 4·8 | 6·3 | 4·5 | | 4·5 | 4·8 | 4·5 | 3·7 | 4·1 | 5·0 |
| Albumin (g.%) | 3·8 | 4·1 | | 3·1 | 3·6 | 3·2 | 4·8 | 3·1 | | 3·1 | 3·6 | 3·2 | 2·8 | 3·1 | 3·2 |
| Globulin (g.%) | 1·8 | 1·5 | | 1·4 | 2·0 | 1·6 | 1·5 | 1·4 | | 1·4 | 1·2 | 1·3 | 0·9 | 1·0 | 1·8 |
| Fasting blood sugar (mg./100 ml.) | 67 | 98 | | 120 | 62 | 100 | | 83 | | | 120 | 100 | 120 | 50 | 62 |
| Urine 17-ketosteroids (mg. per 24 hr.) | 8·0 | 7·0 | | 3·0 | 6·5 | | 1·6 | 3·0 | | | 2·8 | 2·0 | | | 1·8 |
| Eosinophil count (per c.mm.) | 128 | 128 | 80 | 64 | 96 | 128 | 32 | 128 | 0 | 32 | 0 | 0 | 0 | 0 | 32 |

complain, and there was slight oedema of her face, especially of her eyelids. A lumbar puncture was performed, but the fluid was normal and not under pressure. The dose of cortisone was increased, and by the 13th day the oedema of her face had disappeared and she was feeling very well again.

When the patient reached the 38th week of pregnancy, and had then been having treatment with cortisone for 14 days, labour was induced by the introduction of bougies. The pregnancy was terminated because, although the probability of a second convulsion was remote, the foetus did not appear to be growing and signs of toxaemia were still present. Labour was rapid, the first stage lasting nine hours. When she had been 40 minutes in the second stage of labour a normal live female infant—4 lb. 8 oz. (2 kg.)—was delivered by forceps. The duration of the third stage of labour was 10 minutes. The placenta showed numerous white infarcts and also an area of premature separation due to accidental haemorrhage. Progress was now satisfactory, and on the ninth day of the puerperium the blood pressure was 150/95, the urine contained "a trace" of albumin, but no casts or erythrocytes, and there was no oedema. Two days later, however, on the third day after the last dose of cortisone, this patient became apathetic, uninterested in her surroundings, and showed signs of mental disorientation.

During the next few days she exhibited thought-blockage, became suspicious, and developed delusions of persecution; and then became negativistic and refused food. She was examined by Dr. J. Malone, psychiatrist to the hospital, who diagnosed puerperal schizophrenia in an individual of low intelligence. Dr. Malone interviewed her husband and concluded from this talk that she had had a schizoid personality prior to admission and even before she became pregnant. No definite conclusion could be reached on what part, if any, the cortisone had played in the development of schizophrenia, but Dr. Malone thought that it was probably not responsible. The patient was removed to Grangegorman Mental Hospital for insulin-shock treatment under Professor John Dunne, who eight weeks later reported that psychologically her recovery was then complete. The baby survived.

### Case 6 (see Fig. 6 and Table II)

The patient, a woman aged 22, was at the 37th week of her second pregnancy; the first had ended in abortion at three months. She was admitted with generalized oedema of the face, hands, feet, and abdominal wall. Her blood pressure was 160/90, and the urine contained 1+ albumin, numerous hyaline and granular casts, and a few erythrocytes. She had no headache or eye symptoms. For the first six days there was no change. She was kept in bed, and given a low-salt diet and a daily fluid intake restricted to 30 oz. (852 ml.). On the seventh day she suddenly developed a very severe headache with blurring of vision and "spots" before her eyes; there was also marked twitching of her hands and face, and she was extremely restless. She was anaesthetized with intravenous thiopentone and was kept sedated with difficulty during the next 14 hours.

On the eighth day treatment with cortisone was begun. On the ninth day she was definitely improved, and by the 10th day the improvement was marked; she now ate her meals and received visitors, her sight was perfect, the oedema was again less, and she had no headache. On the 12th day there was slight blurring of both disks. She remained very well until the 15th day, when labour was induced by artificial rupture of the membranes. Labour began eight hours later and lasted 11 hours. The foetal heart ceased to be heard late in the first stage of labour, and she was delivered spontaneously of a fresh stillborn infant—7 lb. 3 oz. (3.3 kg.). The third stage of labour was normal. Examination of the placenta showed only a few infarcted areas, and there was no evidence of premature separation of the placenta due to accidental haemorrhage.

The puerperium was normal. The blood pressure fell to 135/80, and the albuminuria disappeared on the fourth day.

Dr. Frank Geoghegan performed a post-mortem examination on the infant. The cause of death was subtentorial haemorrhage. No abnormality was found elsewhere, and all the endocrine glands, including the adrenals, were anatomically and histologically normal.

### Case 7 (see Fig. 7 and Table II)

The patient, a primigravida aged 22, at 34 weeks' gestation, had no relevant past history. She was a mental defective, and was admitted with a blood pressure of 160/110, albumin 1+ in the urine, and moderate oedema of her face and abdominal wall. She gave a history of having been in bed for the previous fortnight. On the second day there was marked general deterioration; she had severe

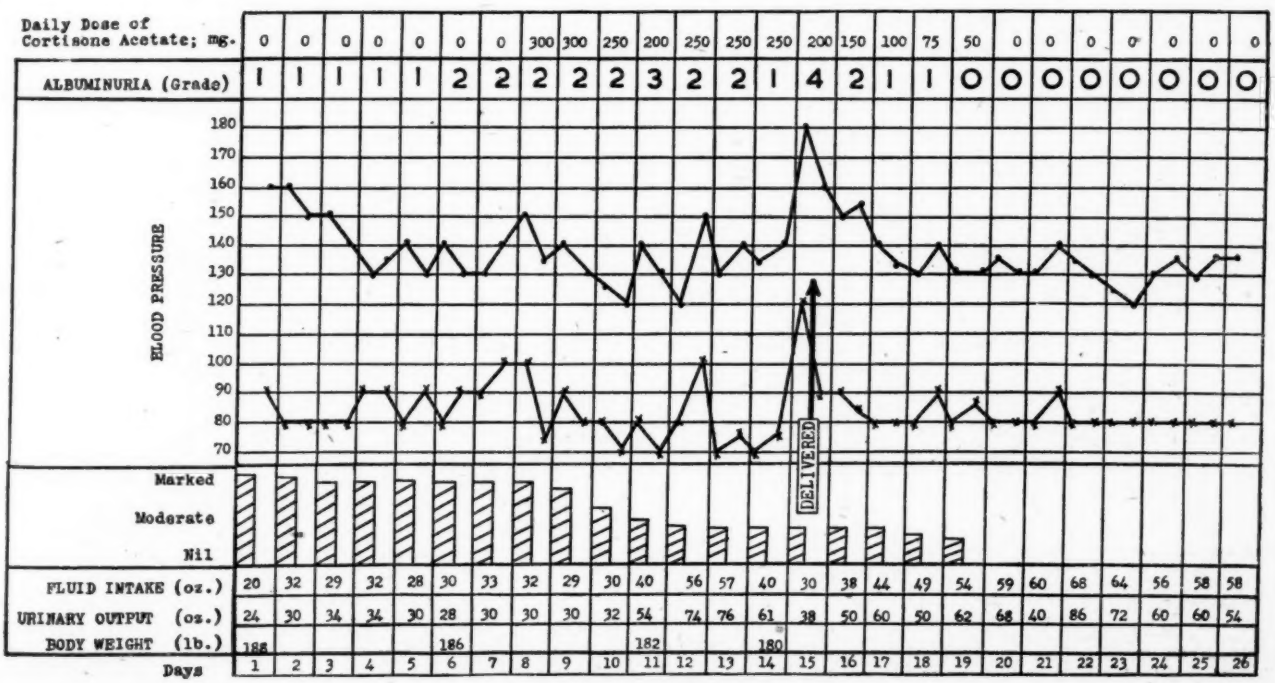


FIG. 6.—Case 6.

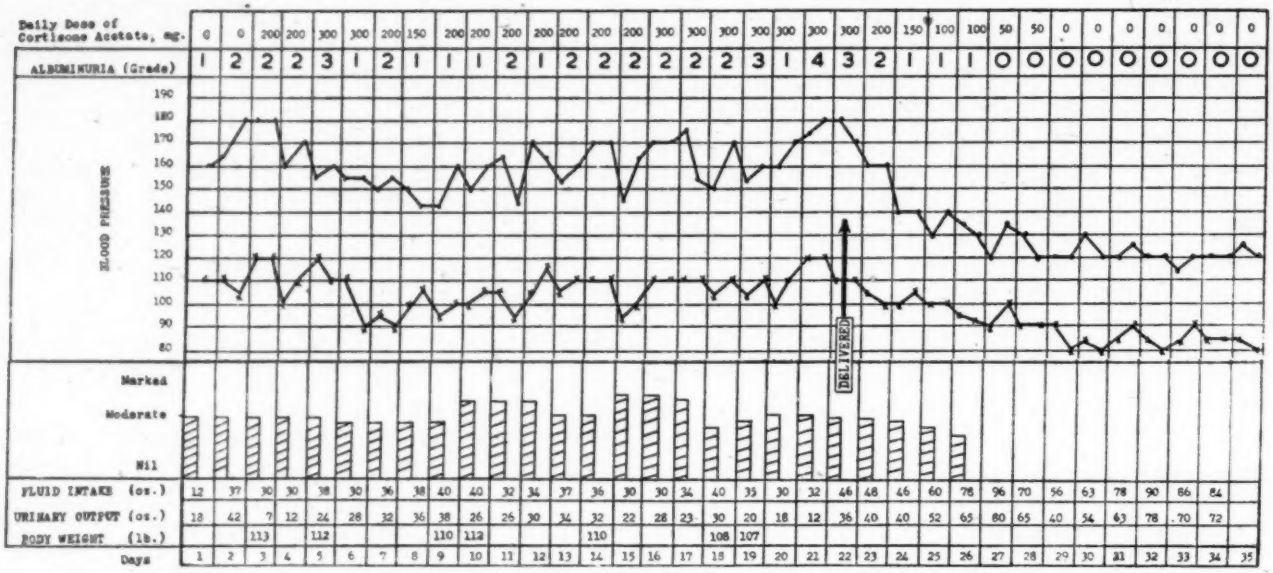


FIG. 7.—Case 7.

headache and "spots" before her eyes, her face was flushed, and she was very restless and irrational. After sedation, and 48 hours after admission, treatment with cortisone was begun. On the third day she was still irrational, she complained of headache and dimness of vision, and her urinary output was only 7 oz. (200 ml.) for 24 hours. By the evening of the fifth day she had improved; on the sixth day she was comfortable and had no complaints. During the next two days the dose of cortisone was reduced, and on the ninth day she was not so well; she complained of headache, there was slight oedema of the face, a fall in the urinary output, and blurring of both optic disks.

On the 10th day she was improved, and up to the time of the onset of labour her condition remained relatively stable. Labour was induced by puncture of membranes on the 19th day and in the 37th week of the pregnancy. Labour was slow, the first stage lasting 44 hours. When she had been one hour in the second stage a normal live infant of 6 lb. (2.7 kg.) was delivered by low forceps. The third stage of labour was normal. The induction-delivery period was 74 hours. The urine was free of albumin from the fifth day after delivery, and the blood pressure on that day was 120/90. The puerperium was uneventful, and the infant made satisfactory progress. The baby survived.

### Case 8 (see Fig. 8 and Table II)

The patient was a 3-para aged 30, at 31 weeks' gestation. The second pregnancy (five years previously) had been complicated by pre-eclamptic toxaemia, and her blood pressure had been 160/100 when she was discharged from hospital three weeks after delivery. The third pregnancy

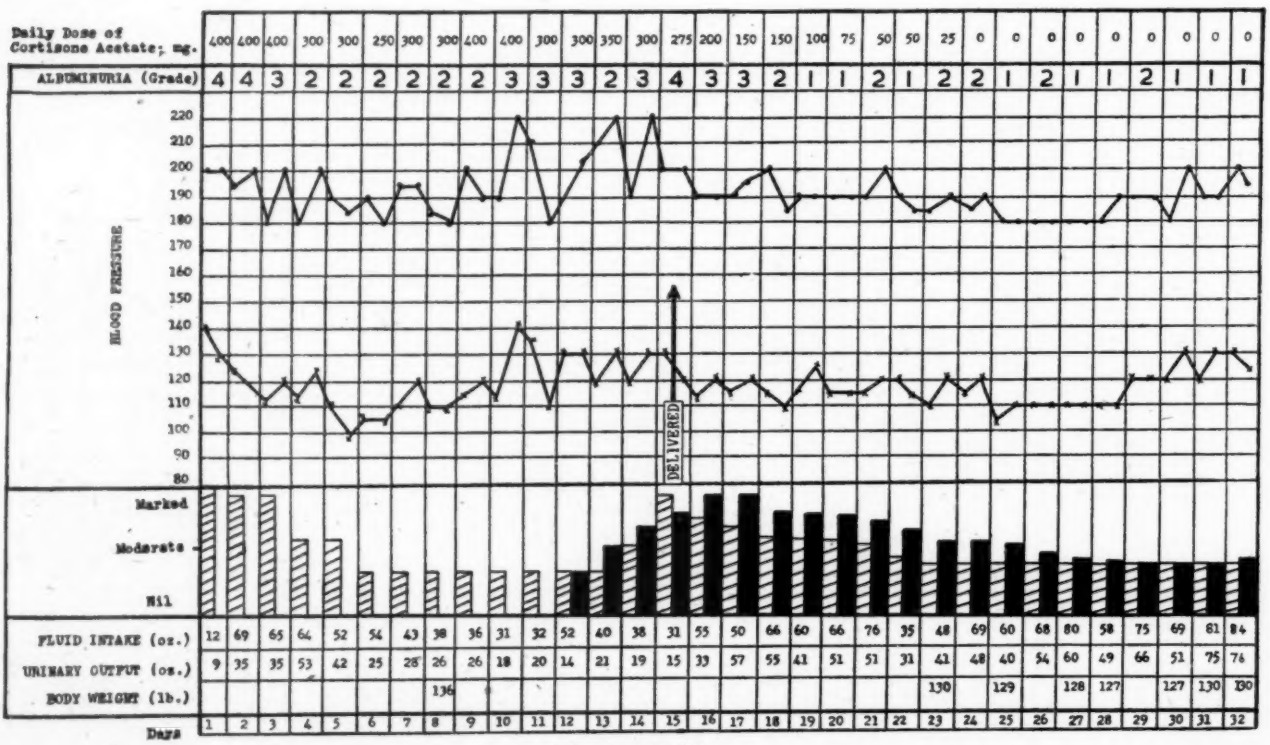


FIG. 8.—Case 8.

(two years previously) had terminated in abortion at 12 weeks. The patient's blood pressure had not been taken during the present pregnancy until admission. During the eight hours before admission to hospital she had had four eclamptic convulsions, and she gave a history of intermittent headaches for a week, and oedema of her feet and legs for a fortnight.

She was admitted to hospital 30 minutes after the last convulsion. Cyanosis was still marked and she was conscious but very restless. She complained of severe headache and blurring of vision. Her pulse was 130 but of good volume, the blood pressure was 200/140, and her heart and lungs were normal. She had marked generalized oedema and the urine contained 4+ albumin. There was papilloedema of both disks, more marked in the left eye (1 dioptre); there were also small haemorrhages to the temporal side of the left disk and a little retinal oedema in both eyes. She was treated at once with intravenous thiopentone and paraldehyde per rectum. Treatment with cortisone was begun two hours after admission. During the night she complained of severe headache and dizziness, and during the first 24 hours her urinary output was low, containing 4+ albumin, some erythrocytes, and numerous hyaline and granular casts.

On the second day of treatment there was some improvement; the oedema was less marked, especially that of her legs; she had no headache but still had some dimness of vision, which was more marked in the left eye. She was anaemic: haemoglobin 64%, red cells 3,690,000 per c.mm. As the urinary output had increased and the body oedema lessened, the dose of cortisone was reduced gradually on the fourth, fifth, and sixth days. During this time she complained of occasional headaches and giddiness, but, in spite of her condition, it was not necessary to press the administration of sedatives. From the sixth day until delivery on the 15th day urinary output was low; the blood urea rose from 30 mg. per 100 ml. on the sixth day to 65 mg. on the 11th day, and on the 10th day the blood cholesterol was 375 mg. per ml.

Because of the persistently low urinary output and the persistently high blood pressure, induction of labour was attempted on the 10th day by the introduction of bougies. Labour, however, did not start until five days later. During this time the urinary output remained low, but otherwise there was no change in her general condition, except that ascites became evident and increased gradually up to the 17th day. (The ascitic fluid contained: total protein, 0.5 g. per 100 ml.; albumin, 0.4 g.; and globulin, 0.1 g.) On the 15th day the patient was delivered of a living male infant—3 lb. 4 oz. (1.5 kg.)—by forceps after 3¼ hours' labour, the indication for forceps being maternal distress. Her blood pressure was 190/120 and the urine contained 4+ albumin. The placenta appeared very unhealthy and contained numerous white infarcts. During the puerperium the blood pressure did not drop much, but the ascites diminished and finally disappeared on the 17th day of the puerperium. The oedema remained well marked in the feet, legs, and lumbar region. Her weight fell only 3 lb. (1.4 kg.). The urinary output was very satisfactory—an average of 50 oz. (1,420 ml.) a day—but albumin was always present, varying from 1+ to 2+. There was no change in the right retina, and the retinal haemorrhages were unchanged. On the 15th day of the puerperium the blood cholesterol was 425 mg. and the blood urea 45 mg. per 100 ml. Two days later the blood urea was 29 mg. per 100 ml. The infant survived.

On the 11th day of the puerperium she was allowed up and given a full diet. The anaemia had persisted and her haemoglobin was then only 51%. She was later removed to the Mater Misericordiae Hospital for further study of her cardiovascular and renal functions. As a result of these investigations it was concluded that this patient had nephrosclerosis with a superadded nephrotic syndrome, and that part at least of her kidney damage antedated the recent pregnancy.

## Discussion

In conversation, Professor Philip S. Hench asked whether the infants after birth showed evidence of cortisone deficiency. We can say that none of them appeared to do so.

In reporting the present eight cases of pregnancy toxaemia treated with cortisone we record facts. We draw no final conclusions, as the cases are too few in number and the variability of results in the treatment of this condition is well known. All we can say on the basis of our present work is that cortisone appears to be a help in the treatment of toxaemia of pregnancy, but further careful studies are necessary on a large number of cases before definite conclusions can be warranted.

In particular it is important that further experience should be gained in the correct use of the hormone in this type of case. In our series it is quite possible that unfavourable results may sometimes have been due to a reduction in the dose of the hormone, and it is also possible that in a few instances where the dose of cortisone was reduced in order to meet a particular situation it might have been more correct to increase it. It now seems likely, in view of our experience with the last three patients, that the standard dose of 100 to 150 mg. a day used in the other cases could have been increased for a time to double this figure with advantage.

In reviewing the eight cases treated certain points seem worth stressing. All cases were seriously ill, with well-marked evidence of toxaemia. One of these cases was put on cortisone immediately after admission, but the other seven were in the hospital for periods varying from 18 hours to 13 days before cortisone treatment was begun. In all eight cases it was found, before cortisone was started, that routine treatment with sedatives was to some degree essential, and in the majority this had to be continuously maintained. By contrast, as soon as cortisone treatment was started the need for sedatives was immediately reduced; in some of these patients none was required until labour started and in others sedatives were needed only to induce sleep at night. This is, in itself, an advance in treatment, for, while sedation is necessary to control restlessness and lessen the risk of convulsions, it carries a definite risk for the baby.

The period of gestation was prolonged by one to four weeks on cortisone treatment. In the absence of cortisone the routine treatment in many of the patients would have been termination of the pregnancy at about the time cortisone treatment was started. The prolongation of gestation with cortisone in three of the cases was probably an important factor in enabling their premature babies to be born alive, although two of them died later.

It should be stressed that the striking improvement after the institution of cortisone treatment in each case was in the clinical condition of the patient. Headache was relieved, vision when affected was improved, restlessness was controlled, and both the patient and her friends were quite definite that she was much better. On the other hand, the effect on blood pressure was disappointing. In two cases in which oedema had been reduced its place was taken by ascites; in two others the oedema, which had been diminished by cortisone treatment, later increased at the same time as the ascites

became apparent. The development of ascites is in itself a problem of considerable interest. Most of the results of biochemical investigation were neither striking nor consistent. There is some evidence that administration of cortisone caused an increase in serum potassium. In four cases the values for uric acid decreased significantly on cortisone treatment, but in the others this change was not observed. The figures for plasma protein were not consistently related to cortisone. Except in three cases in which the initial figure was already low, the values of 17-ketosteroid excretion showed a fall related to cortisone therapy, which may be due to inhibition of the anterior pituitary by the cortisone with consequent reduction of adrenal cortical activity. It would seem from these results that cortisone is not converted to a 17-ketosteroid type of compound, at least in late pregnancy. Eosinophil counts, when raised, generally showed a marked fall on cortisone therapy—a result which has been repeatedly recorded by other workers.


## Summary

Eight cases of toxaemia of pregnancy were treated with cortisone by intramuscular injection.

The ages of the patients varied from 22 to 42 years. Five were primigravidae; in one it was her second pregnancy; and in two it was their fourth pregnancies. The period of gestation at the start of cortisone treatment was 37, 40, 28, 31, 36, 37, 34, and 31 weeks, respectively.

All patients, when admitted, were seriously ill, with raised blood pressure and albuminuria. Five had well-marked oedema. One of the cases had had four eclamptic convulsions immediately preceding admission, one had had one convulsion before admission, and one had a convulsion during labour. In all seven cases in which the foetus was viable the indications were for a termination of the pregnancy on, or soon after, the patient's admission. In the eighth case the foetus might have been expected to die.

Cortisone treatment was continued for 27, 5, 14, 8, 14, 7, 17, and 15 days, respectively, before the onset of labour.

In all cases the outstanding feature following treatment was the considerable clinical improvement. The need for sedatives was reduced, headache was relieved, oedema, when present, was reduced, albuminuria was usually diminished, and diuresis seemed to be promoted. Blood pressure was not significantly affected. Ascites developed in five cases.

In three cases labour started spontaneously, and in five it was induced.

Seven of the patients were delivered of live babies. In the remaining case the baby was stillborn, the cause of death being a subtentorial haemorrhage. Two of the babies were premature and died, but in one of these post-mortem examination showed an intracranial haemorrhage.

Five of the patients left hospital apparently normal. One was transferred 34 days after delivery to a general hospital, where she died of congestive heart failure. One developed schizophrenia on the fifth day after cortisone treatment was discontinued. The last case was also transferred to a general hospital for investigation of her cardiovascular and renal systems.



We are grateful to Dr. Maurice Hickey, of the Mater Misericordiae Hospital, Dublin, and to Dr. Frank Geoghegan, of the National Maternity Hospital, Dublin, for having carried out some of the biochemical estimations on samples of blood from these patients, and to Dr. T. E. T. Bradshaw, of the Department of Physiology, Royal College of Surgeons in Ireland, for having carried through all the estimations of 17-ketosteroids in his laboratory at the Rotunda Hospital, Dublin. The charts were drawn by Mr. Ronan Kernan, of the Department of Anatomy, University College, Dublin.

We wish to acknowledge our great indebtedness to Messrs. Merck and Co. for having made available the supplies of cortisone used in the treatment of these cases through Dr. J. M. Carlisle, their medical director, and for the continuous fund of information and advice which was always at our disposal. A considerable proportion of the cortisone used was generously given free of charge. We would also like to acknowledge our appreciation of the personal interest shown in this work by Professor Philip S. Hench, of the Mayo Clinic, and by Dr. J. M. Carlisle during their visits to Dublin.

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# POST-TRAUMATIC DISTURBANCE OF HYPOTHALAMIC FUNCTION


BY

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The detailed anatomy of the hypothalamic region and its connexions with the cortex of the neopallium have been described by various authors (Rioch, 1931; Le Gros Clark and Boggon, 1933; Walker, 1938; Meyer *et al.*, 1947; Mettler, 1947), while the work of Fulton *et al.* (1940) has enabled us to form a concept of hypothalamic function which, though admittedly incomplete, has added considerably to our knowledge of some of the mechanisms by which this ancient portion of the brain reinforces and co-ordinates certain bodily reactions to physiological and psychological stimuli coming from an ever-changing milieu.

It is known that several well-defined pathological entities (such as diabetes insipidus, obesity, abnormal somnolence, and genital atrophy) may arise after damage either to hypothalamic nuclei or to their connexions with the neurohypophysis, but it is perhaps not so widely recognized that fixed lesions in the central nervous system outside the hypothalamus can give rise to marked disturbance of hypothalamic function, with repeated displays of exaggerated hypothalamic activity (Fulton and Ingraham, 1929; Penfield, 1929; Engel and Aring, 1945).

The hypothalamic syndrome described below is of interest for several reasons. Two of its features are common to the syndrome described by Kleine (1925) and Levin (1936), and are periodic in nature. The

condition is post-traumatic in origin, and its clinical features differ in some respects from those commonly found in post-traumatic lesions.

The number of reported cases of hypothalamic disorders following head injury is not large. This may, however, be due to the fact that in most of the reported cases the diagnoses have been made more simple by the presence of fairly obvious static signs and symptoms indicating lesions in the hypothalamus itself—that is, diabetes insipidus, obesity, and disorders of sleep. The significance of less obvious post-traumatic sequelae such as disturbances of autonomic function may often pass unrecognized, as these disturbances are not discoverable by the usual routine methods of examination of the nervous system. In the undermentioned case, for example, no clinical investigation was carried out until almost four years after the occurrence of the original head injury.

As this case did not come under my care until several years after the initial injury, the description of the onset and the early manifestations of the syndrome is based on the observations of the boy's mother. The latter is a reliable witness and an accurate observer, with the added advantage of a training as a nurse, and from the account given by her there is every reason to believe that the features now present existed from an early stage after the initial injury.

The syndrome is made up of the following abnormalities: thermohyperaesthesia; periodic abnormal hunger; periodic psychomotor restlessness; disturbances of autonomic function and abnormal reactions to certain drugs; occasional bouts of pyrexia associated with intestinal colic, nausea, vomiting, and bladder irritability; and a compulsive habit of chewing and swallowing various articles and substances.

## Case History

The patient, a boy aged 11, was a healthy child until the age of 4½, when he sustained the head injury mentioned below. He began to walk and to talk at the average normal age, and did not suffer from fits or convulsions in infancy. There is a clean family history, and the home background is a happy and normal one. He has two older brothers and one younger sister, all of whom are intelligent and likeable children.

On the morning of October 12, 1943, when running to school, he tripped and fell forward, striking the base of his forehead forcibly against the edge of a stone kerb. He was momentarily stunned and a massive haematoma developed over the frontal bone. He was taken to the local hospital and kept there under observation for three weeks. Unfortunately the case notes made at the time are incomplete, and, apart from the fact that there was no bony injury shown on an *x*-ray film of the skull, little information can be gained from the clinical observations then recorded. He was kept in bed for a further week after returning home and did not go back to school until the beginning of the next term. About six weeks after his discharge from hospital his mother noted the development of changes in behaviour and the onset of the compulsive habit which he now exhibits. During the next few months, and especially during the warm weather in the summer of 1944, other abnormalities were noticed by his parents. These still persist, and are referable to a disturbance of autonomic function.

The first abnormality noticed was the onset of the chewing and biting of his nails and fingers, a habit to which he had not previously been addicted. In the next month or so he had begun to chew and swallow a variety of substances—namely, his clothes, the edges of his cuffs and pullover, his handkerchiefs, and pieces of the bedclothes. He began to eat portions of thread, string, and plasticine, later vomiting matted masses of these substances. Pieces of chalk and crayons were also eaten, and on occasion he has been found with small metal objects in his mouth. This abnormal behaviour appeared to be intermediate in nature between a reflex and a voluntary action, for it was noted to occur even when his attention was wholly concentrated on some subject of absorbing interest. It did not seem especially to be connected with any situations which, in a child, might give rise to mild anxiety, but appeared at intervals for no apparent reason, and can now be brought on at any time in intensified form by the action of certain drugs.

The second abnormality noted was one affecting appetite. This was also periodic, and when the urge developed his hunger was almost insatiable. Tachyphagia was a prominent feature of a feeding ritual in which he showed a preference for certain foods similar to that described by Arieti (1945) as occurring in certain cases of mental disease. During a recent attack he consumed a 14-oz. (400-g.) loaf before his lunch, at which he proceeded to eat as much as both his brothers. This was followed by a large apple and a glass of milk, and after this he still asked for more.

About this time it was observed that he sweated heavily about the face when eating. This phenomenon was much more marked on the right side of the face, and was accompanied by flushing of the skin. Dilatation of skin vessels was maximal on the ears and along the border of the lower jaw. Sweating was most pronounced in the periorbital region and along the side of the nose and the upper lip. It is occasionally accompanied by lacrimation from the right eye. The sight, smell, and even the thought of certain articles of food will cause sweating on the face, and it can be rapidly elicited by the taste of bitter substances.

During hot weather, on physical exertion, and when emotionally excited, profuse sweating occurs over the whole body. Sweat literally streams from him, and during very hot weather he becomes somewhat pinched and dehydrated in appearance. It is stated that on one occasion, when a particularly profuse bout of sweating occurred, a tingling sensation was felt in the skin of the face and scalp, and the sweat was faintly tinged with blood. Profuse sweating occurs over the face and scalp for an hour or so before he goes to sleep.

Coincident with the periods when the chewing-swallowing habit emerges a marked restlessness occurs, and the autonomic over-reactions become more noticeable. He seems quite unable to keep still or to concentrate on any subject for any length of time, nor will he allow the other members of his family to do so. During these attacks he becomes a trial to his parents and to his older brothers, who are unable to get on with their studies owing to his continual interference with them. This restlessness can be brought on at any time, and in a marked degree, by giving small doses of certain drugs.

The attacks of hyperthermia associated with intestinal colic have occurred both in cold and in hot weather. They are accompanied by nausea and, at times, vomiting. Frequency of micturition and marked general irritability are present during the attacks. The temperature has ranged from 100 to 102.5° F. (37.8 to 39.15° C.), and there is marked flushing and sweating. The duration of attacks in the past has been from 24 to 48 hours. The attack I saw was associated with minor infection (coryza), and it is felt that previous attacks had a similar aetiology.

The only disturbance noted affecting sleep is a delay of an hour or so in the onset of sleep after going to bed. This delay is more prolonged when attacks of restlessness are present, and at these times he showed a resistance to the action of barbiturates, a dose of 2 gr. (0.13 g.) of sodium amylobarbitone or 1½ gr. (0.1 g.) of quinalbarbitone sodium having but little effect.

During the periods of restlessness he is easily roused to anger and becomes aggressive. His aggressiveness is always directed against boys bigger and older than himself. He is kind to smaller children and animals, and there are no traits of a cruel nature. He is an intelligent boy, and is in an advanced class at school. He has the usual hobbies and traits common to boys of his age, is a keen philatelist, is fond of music, plays the piano, and sings in the church choir.

### Investigations

Physical examination by ordinary methods revealed nothing abnormal: weight, 69 lb. (31.3 kg.); height, 53½ in. (136 cm.); span, 54 in. (137 cm.). Both testes are in the scrotum. His blood pressure has varied on successive examinations from 114/70 to 130/80.

*Special Examinations.*—Urine acid: specific gravity 1016; no albumin or sugar; chloride content, 960 mg. per 100 ml. The blood Wassermann reaction was negative. Radiographs of the skull did not reveal any abnormality, the size and shape of the pituitary fossa being within normal limits. An electro-encephalogram showed "some instability, but no more than would be expected in a boy of his age." A fractional test meal showed an acid curve on the lower side of the average normal range. A barium meal showed that the stomach emptied in less than an hour, and that the meal had reached the middle of the transverse colon in six hours.

### Investigation of Temperature Regulation

There is a tendency to hypothermia, with an average daily reading of 96.4° F. (35.8° C.) (oral). Thermohyperaesthesia is present, for it has been noted that since shortly after his head injury he has never been able to stand with comfort a bath at a temperature of over 99° F. (37.2° C.).

*Reaction to Bath at 103° F. (39.4° C.)*

| | °F. | °C. |
|---|---|---|
| Oral temperature before immersion .. .. | 96.2 .. | 35.7 |
| " " after 5 minutes' immersion .. | 100.2 .. | 37.9 |
| " " after 10 minutes' immersion .. | 101.6 .. | 38.7 |

When the oral temperature reached 98.4° F. (36.9° C.) marked flushing of the face occurred, and at 100.2° F. (37.9° C.) marked flushing accompanied by profuse sweating was observed. He was removed from the bath after 10 minutes, and within a further 15 minutes his oral temperature had fallen to 98.2° F. (36.8° C.).

*Reaction to Bath at 85° F. (29.4° C.)*

| | °F. | °C. |
|---|---|---|
| Oral temperature before immersion .. .. | 98.2 .. | 36.8 |
| " " after 5 minutes' immersion .. | 96.0 .. | 35.6 |

Shivering and vasoconstriction of skin vessels then occurred, and in the next four minutes his oral temperature had risen to 97.2° F. (36.2° C.). The reactions observed were "full-blown" ones, and can be regarded as exaggerated in view of the fact that neither of the bath temperatures to which the patient was exposed appears to be deserving of the intensity of the response exhibited.

I saw only one attack of hyperthermia—101.5° F. (38.6° C.)—associated with intestinal colic. It occurred at the onset of an attack of coryza, and was accompanied by marked restlessness, flushing, and sweating. Bladder irritability was also present, and the chewing habit was well in evidence, the patient having eaten away a hole in the sheet. The symptoms were easily controlled by tepid sponging, and during one period of severe intestinal colic immersion in a tepid bath quickly relieved this symptom.

The hyperhidrosis affecting the face is readily elicited by the smell or sight of a bitter food (lemon), while application of bitter substances to the tongue produces a similar effect.

### Reactions to Drugs

Abnormal hunger is usually associated with gastro-intestinal hypermotility. In an effort to counteract this, and to prevent the occurrence of attacks of this nature, a dose of 50 mg. of "syntropan" was given by mouth three times a day, and continued over a period of several weeks. During this time he did not develop any attacks of abnormal hunger, though he was still restless on occasion, but his habit of chewing was a little less in evidence. He has since been kept on 5 minims (0.3 ml.) of tincture of belladonna, three times a day, and his appetite has been for the most part normal.

As amphetamine has been observed to counteract the psychomotor restlessness in some cases in which this feature is present, he was given a single initial dose of 2.5 mg. This produced the most marked attack of restlessness he had ever had. His behaviour resembled that of a caged animal; he ate a hole in the sheet and gnawed the embroidered border off his pillow-cases. The restlessness subsided in about six hours. Small doses of ephedrine produce a less marked effect of similar nature.

Diphenhydramine hydrochloride ("benadryl") has been reported to be effective in relieving spasm of smooth muscle (Loew *et al.*, 1946), and it was considered worth while to observe its effect in this case. Accordingly, 100 mg. daily, divided into three doses, was given for five days. Its effect was similar to that of amphetamine: he showed very marked restlessness, began to chew his clothing, bit his nails down to the quick, and chewed the skin from the tips of his fingers.

A course of phenytoin sodium ("epanutin") produced no effect whatever, while phenobarbitone simply blurred the general symptom picture.

A careful inquiry from the child's parents and teachers revealed no evidence of psychological maladjustment. He was a happy and popular boy with a good school record; he had always faced up to all his problems, and had never attempted to make use of his symptoms in an effort to evade unpleasant situations. He admits to the usual mild anticipatory anxiety before school examinations and the like, but the external expressions of this mood appear to be exaggerated out of all proportion to the depth of feeling tone with which they are associated.

## Clinical Features

Two of the clinical features of this case merit further comment.

1. *The Similarity of Effects Produced by Diphenhydramine to those Effected by Sympathomimetic Drugs.*—It is not easy to explain why this should be the case. From the chemical constitution of this compound one would not expect it, or its degradation products, to have any direct sympathomimetic effect. Its most common side-effect is the production of drowsiness, and this is no doubt central in origin, but there is no clear evidence of the precise mechanism by which this is brought about. It seems reasonable to surmise that part of the central action of diphenhydramine is concerned with inhibition of the parasympathetic side of the autonomic nervous system, and that a relative preponderance of the sympathetic side is thus effected.

2. *The Abnormal Reactions to Pyrexia Associated with Minor Infection.*—These reactions are modified by the fact that the thermal stimulus is in this instance a sustained one. We seem to be dealing here with a mass reaction affecting the anterior hypothalamus, for, in addition to the normal response to hyperthermia (flushing of the skin and sweating), there is frequent emptying of the urinary bladder, and abdominal colic and vomiting due to gastro-intestinal hypermotility.

The work of Ranson (1940) and Ranson and Magoun (1939) indicates that the centres which prevent overheating are situated in the suprachiasmic and preoptic areas; but it has also been shown (Kabat, Ranson, and

Magoun, 1934) that in the preoptic area are cell masses concerned with contraction of the urinary bladder, and there is experimental evidence that increased gastro-intestinal activity follows stimulation of the anterior hypothalamus (Massermann and Haertig, 1938).

## Discussion

In the patient whose case is described above there is exhibited a series of exaggerated somatic and vegetative reactions to physiological and psychological stimuli. Some of the somatic features bear a resemblance to disorders of behaviour, and the emergence of these latter features can be brought about by the administration of sympathomimetic drugs. Their periodic emergence in the past was no doubt due to increased activity of the sympathetic side of the autonomic nervous system. It is evident from the foregoing clinical findings that there has been preserved the functional integrity of the various hypothalamic centres which, by discharging into descending pathways, produce the responses described; and, in the absence of any evidence of infundibulo-tuberal damage—that is, diabetes insipidus or obesity—it can be safely assumed that the hypothalamus itself is intact. Some explanation, however, must be sought for the uninhibited nature of the reactions observed.

Disturbances of hypothalamic function, which may be permanent or transient in nature and mild or profound in degree, are observed to result from lesions in areas outside the hypothalamus. These lesions may be produced by surgical intervention for experimental or therapeutic reasons, or may occur as a result of disease processes. (It is customary to regard as release phenomena the abnormal vegetative and somatic patterns which emerge after damage either to those areas of the cortex in which autonomic functions are represented or to the indirect pathways by which these areas are connected with the hypothalamus. By this it is assumed that the neopallial cortex exercises an inhibitory or controlling effect on the central levels of autonomic function.)

Marked hypothalamic dysfunction has been described (Engel and Aring, 1945) in a case in which an old-standing lesion had affected the dorso-medial nucleus, internal medullary lamina, and the lateral nucleus of the right thalamus. Periodic displays of exaggerated hypothalamic activity occurred mainly in response to situations provoking anxiety, and an interesting feature of the vegetative reactions was the occurrence of hyperhidrosis on the side of face contralateral to the thalamic lesion. That the patient also showed marked psychological maladjustment is not surprising in view of the important part played by the thalamus and its connexions in personality organization.

It has been shown (Messimy, 1939) that in animals marked motor restlessness, abnormal hunger, and exaggerated reactions to sympathomimetic drugs occur after severance (by bilateral excision of the prefrontal regions) of the indirect connexions between the prefrontal cortex and the hypothalamus; and Reitman (1946) has described changes in autonomic balance in man, following prefrontal leucotomy, in which operation connexions between the prefrontal region and the dorso-medial nucleus of the thalamus are severed. In the cases described by Reitman the changes noted were transient ones, while in Messimy's animals the disturbances observed "tended to pass off with time," this regeneration of function after damage being in accord with the behaviour of the brain as a whole.

More profound and more slowly subsiding changes in hypothalamic activity are seen in decorticate animals—that is, animals in which all portions of the brain above the hypothalamus have been removed. It has been observed (Bard, 1929) that in decorticate cats violent motor and autonomic reactions accompanied by widespread activity of the sympathetic nervous system occur in response to physiological stimuli. As the motor and autonomic reactions exhibited are similar to those which characterize rage in the intact animal, the phenomenon is known as "sham rage." It has been noted that when left undisturbed these decorticate animals exhibit alternating periods of repose and activity (Hinsey, Ranson, and McNattin, 1930), and the ultimate subsidence of "sham rage" reactions in chronic decorticated animals has been observed by Kennard (1945). As phylogenetic progression has brought about representation of autonomic functions at cortical levels, it is to be expected that after removal of these higher controlling levels uninhibited reactions would occur when the hypothalamus is excited by physiological stimuli. The eventual subsidence of the "sham rage" reaction is regarded by Kennard as a manifestation of homoeostasis, which is probably brought about by adjustment of the entire remaining autonomic system.

A more interesting observation, however, is that effects similar to and more prolonged than those brought about by decortication can be produced in intact cats by the placing of bilateral lesions just in front of the optic chiasma (Fulton and Ingraham, 1929), and that in monkeys states akin to "sham rage" can be produced by bilateral lesions placed in the same areas (Fulton, 1947, personal communication). Associated with the "rage" there is evidence of diffuse discharge of the sympathetic nervous system. It is evident that in these areas are situated pathways by means of which an overall control of hypothalamic activity is exerted, and that the release phenomena resulting from lesions affecting these pathways are more prolonged and profound than those which follow section of the indirect cortico-hypothalamic connexions which relay in the dorso-medial nucleus of the thalamus.

In the case described above, signs of exaggerated hypothalamic activity following head injury have persisted for over six years; the syndrome features, both somatic and vegetative components, and the somatic components can be readily elicited by the administration of sympathomimetic drugs. (It appears that a slow subsidence of symptoms is taking place, for some of the features are stated to be now less marked than formerly.)

The nature and persistence of the abnormal reactions described, and their association with increased sympathetic activity, would justify a conclusion that the initial head injury had produced a contusion in the area just anterior to the chiasmal region, that the damage was bilateral in extent and possibly more severe on one side than on the other, and that the sequelae are manifested in the syndrome described.

The factors underlying causation of the chewing–swallowing habit are obscure. As the habit invariably

accompanies the restlessness produced by sympathomimetic drugs, there is reason to regard it as a release phenomenon, and from its unusual and frankly regressive nature one would surmise that it is mediated through some phylogenetically ancient pathways.

The significance of primitive habits of this nature has been discussed by Arieti (1945). He notes that what he terms the "placing into mouth" habit is found in children approximately 1 to 2 years of age, that it is also found in advanced cases of schizophrenia, and that in these latter cases it is often accompanied by bulimia, tachyphagia, and a stereotyped feeding ritual. He considers that the habit represents a primitive response, in the mechanism of which a short-circuiting takes place between the functions of reception and those of reaction, with exclusion of the usual normal paths which involve higher centres, and suggests that instead of the normal path a circuit is used similar to that involved in the relatively primitive physiological complex which Edinger has called the "oral sense." He has also noted the development of this habit in a case following bilateral prefrontal lobectomy. A similar habit has been found in cats after removal of both frontal poles (Langworthy, 1944), while Von Braunmühl and Leonhard (1934) have reported its occurrence in cases of Pick's disease. The habit is often observed in amentia and dementia from various causes.

Though this release phenomenon has been found to emerge after damage or degeneration affecting the prefrontal areas in man, there is evidence that it may represent a primitive archipallial expression. Grünthal (1947) describes the phenomenon (accompanied by a return of the sucking reflex) in a woman, aged 62, in whom the only evidence of cerebral damage found at necropsy was a circumscribed bilateral degeneration of the cornu Ammonis, and it has long been noted that marked perversion of feeding habits occurs in the early stages of rabies in dogs, in which disease the cornu Ammonis is severely affected. It would thus seem that efferent pathways from the hippocampus can exert an inhibitory action on lower centres in the rhinencephalon concerned with simple feeding reflexes, and it is possible that this inhibitory function in human primates is partially vested in the prefrontal areas, presumably in those portions of the orbital area from which the direct pathways to the hypothalamus arise. Exaggerated hypothalamic activity might well be associated with a spill-over of excitation into the primitive pathways described above, and these, by discharging into subthalamic motor centres, would give rise to those movements which form the somatic framework of the "placing into mouth" habit.

### Summary and Conclusions

A case is reported in which disturbance of hypothalamic function has persisted for over six years following head injury.

The various components of the syndrome exhibited are described, and an account is given of the patient's reaction to various drugs.

The neuro-physiological mechanisms which govern certain features in the syndrome are discussed.

A possible explanation is advanced in accounting for a primitive habit which forms part of the clinical picture in the case described.

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# PREVENTION OF HORMONAL EOSINOPENIA AND LYMPHOPENIA BY INHIBITION OF CLOTTING IN BLOOD

## PRELIMINARY REPORT

BY

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It has already been well established that phenomena of eosinopenia and of lymphopenia follow the administration of potent preparations of adrenocortical steroids with C11 oxygenated, or the application of hormones or agents which stimulate their endogenous secretion. The mechanism and the meaning of these phenomena are not clearly understood. Dougherty *et al.* (1944) demonstrated that the amount of gamma-globulins in the blood plasma rose significantly, parallel with the degree of lymphocyte diminution after the administration of A.C.T.H. or of cortisone or cortisone-like steroids. At the same time the titre of the specific antibodies also increased significantly. They concluded from these findings that disintegrating cytoplasm of the lymphocytes is the source of gamma-globulins, which are closely related to the specific antibodies, and that they are discharged from lymphocytes under the activity of the adrenocortical steroids. Those authors' observations, however, were not confirmed by others (De Vries, 1950), since the N-antibodies did not rise in the blood at the time of the lymphopenia after A.C.T.H. injection. The pheno-

*Data of the Experiments*

| No. | Initial Values | | | | Heparin in Anticoagulant Int. Units | Clotting Time 10 Min. after Heparin Injection | Eosinopenic Hormone in mg. | Values at End of Fourth Hour | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Circulating Eosinophils per c.mm. | Circulating Lymphocytes per c.mm. | Circulating Polymorphs per c.mm. | Clotting Time in Minutes | | | | Circulating Eosinophils per c.mm. | Circulating Lymphocytes per c.mm. | Circulating Polymorphs per c.mm | Clotting Time in Minutes |
| 1 Man a | 241 | 1,840 | 2,700 | 14 | 0 | — | A.C.T.H., 30 mg. | 100 | 1,240 | 9,020 | 10 |
| 1 Man b | 135 | 1,353 | 2,337 | 12 | 125,000 | < 4 hr. | A.C.T.H., 30 mg. | 214 | 3,760 | 12,760 | < 4 hr. |
| 2 Man a | 115 | 2,300 | 2,200 | 16.5 | 0 | — | A.C.T.H., 45 mg. | 63 | 2,038 | 7,738 | 10 |
| 2 Man b | 118 | 1,640 | 2,000 | 16 | 125,000 | < 4 hr. | A.C.T.H., 45 mg. | 152 | 5,320 | 9,570 | < 4 hr. |
| 3 Man a | 106 | 2,700 | 2,385 | 6.5 | 0 | — | Adrenal, 5 mg. | 10 | 2,180 | 13,944 | 4 |
| 3 Man b | 136 | 2,385 | 3,264 | 4 | 75,000 | < 4 hr. | Adrenal, 5 mg. | 108 | 3,132 | 7,320 | < 4 hr. |
| 4 Man a | 729 | 3,888 | 3,480 | 7 | 0 | — | Adrenal, 5 mg. | 260 | 3,900 | 20,280 | 5 |
| 4 Man b | 268 | 1,824 | 3,420 | 7 | 125,000 | < 4 hr. | Adrenal, 5 mg. | 293 | 3,150 | 18,000 | < 4 hr. |
| 5 Dog a | 521 | 1,806 | 5,590 | 6 | 0 | — | Cortisone, 20 mg | 390 | 1,300 | 10,400 | 4 |
| 5 Dog b | 304 | 1,380 | 6,716 | 7 | 15,000 | < 4 hr. | Cortisone, 20 mg. | 759 | 4,600 | 16,100 | < 4 hr. |
| 6 a | 1,312 | 4,100 | 9,840 | 5 | 0 | — | Insulin, 50 units | 483 | 1,539 | 13,680 | 3 |
| 6 b | 738 | 4,235 | 11,300 | 4 | 30,000 | < 4 hr. | Insulin, 50 units | 858 | 3,042 | 18,450 | < 4 hr. |
| 7 a | 620 | 3,255 | 5,185 | 9 | 0 | — | Insulin, 50 units | 279 | 2,011 | 6,500 | 6 |
| 7 b | 600 | 3,200 | 5,910 | 5 | 25,000 | < 4 hr. | Insulin, 50 units | 545 | 3,640 | 13,280 | < 4 hr. |
| 8 | 647 | 2,184 | 6,158 | 7 | 25,000 | < 4 hr. | 0 | 847 | 2,914 | 5,264 | < 4 hr. |
| *9 | 32 | 2,140 | 7,918 | 8 | 25,000 | < 4 hr. | 0 | 243 | 3,870 | 5,400 | < 4 hr. |
| 10 | 522 | 5,220 | 7,975 | 9 | 20,000 | < 4 hr. | 0 | 860 | 5,332 | 10,492 | < 4 hr. |

a = controls; b = experiment series. Cortisone acetate (Merck and Co., batch A009125); A.C.T.H. (Armour, Standard LA-1-A, lyophilized).
* The figures of the last four columns were obtained after end of the twenty-fourth hour.

menon of eosinopenia caused by the injection of a potent A.C.T.H. preparation is of such a constant character that it induced Thorn *et al.* (1948) to regard it as a test for the adrenocortical function.

In the course of the study of the fate of eosinophils during hormonally produced eosinopenia, a close relation between blood clotting and the disappearance of eosinophils and lymphocytes has been detected.

In the present experiments the process of clotting in the blood was entirely prevented by intravenous heparin in a dose of 1,560 i.u. per kg. body weight. During the whole experimental period—that is, four hours—another fourth of the initial dose of heparin was given in order to maintain complete incoagulability. Ten minutes after the administration of the first dose of heparin the eosinopenic hormones were injected and cytological analysis of the peripheral blood was made at the end of the fourth hour. Cortisone acetate used in these experiments was in the form of saline suspension with 1.5% benzyl alcohol as preservative.

From the data shown in the table one can postulate that the phenomena of eosinopenia and lymphopenia were completely eliminated or significantly diminished, or that the number of the circulating eosinophils and lymphocytes significantly rose by the inhibition of blood coagulation. In three cases (dogs Nos. 8, 9, and 10) heparin given in the same dosage without a following injection of eosinopenic hormones caused a significant rise in the number of circulating eosinophils.

The explanation of these phenomena lies in the two apparently independent actions of heparin and eosinopenic hormones. Heparin mobilizes the tissue eosinophils arrested in the lymphoid tissue during the interaction between antigen carried by eosinophils (Godlowski, 1948) and specific antibodies discharged from lymphocytes (Dougherty, 1944), shifting them into the circulation; this action is responsible for the rise in circulating eosinophils after heparin injection. Eosinopenic hormones, on the other hand, exert a direct eosinolytic action, causing their disintegration in the circulating blood. The rate of these two actions and the amount of the available eosinophils arrested in the lymphoid tissues determine whether eosinopenia will occur or whether circulating eosinophils will rise despite the eosinolytic action of the eosinolytic hormones.

In the controls the normal clotting time was slightly shortened by the application of the eosinopenic hormones; this can be seen in the table.

A detailed report of the correlation between clotting and elimination of hormonal eosinopenia and lymphopenia, and the implication of this finding in the mechanism of the action of the pituitary–adrenocortical system, as well as an explanation of the mechanism of the eosinolytic action of the eosinopenic steroids, will be published elsewhere at an early date.

I wish to thank the Medical Research Council for the supply of A.C.T.H. and cortisone. I am also indebted to Professor A. M. Drennan for his advice and criticism throughout this investigation.

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# PATHOGENESIS OF MITRAL STENOSIS

BY

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[WITH PHOTOGRAVURE PLATE]

Little attention has been paid in modern times to the pathological changes which underlie the progressive nature of the stenosis occurring in rheumatic mitral disease. This problem has now become of practical importance, because with modern cardiac surgery it is possible to obtain direct relief of the condition by operation on the affected valve.

## Current Theories

There are two main views regarding the pathogenesis of chronic rheumatic valvular thickening and stenosis. Rokitansky (1852) was of the opinion that the valves became thicker in consequence of the deposition on the surface of the cusps of layers of a morbid substance from the blood which becomes converted into fibrous tissue. He also believed that this same process caused the cusps to become adherent to one another by means of repeated deposition in the commissures between them. On the other hand, the usual present-day conception of the process attaches little significance to organization of fibrin on the surface of the valve. Rather it is thought that the necrosis and inflammation which go on within the substance of the valve cusps cause the cicatricial contraction. Coombs (1924) described this process as a purse-string gradually tightening around the orifice of the valve. I believe that there is ample evidence to show that progressive post-rheumatic valvular thickening and development of mitral stenosis are due, at least in part, to organization of repeated deposits of fibrin on the surface of the valve and in the commissures between the cusps as described by Rokitansky, and that it is not necessarily dependent upon the more generally accepted process of post-inflammatory cicatricial contraction within the substance of the valve.

## Evidence

It is not now in general dispute that the thrombi forming the typical vegetations of acute rheumatic endocarditis become covered by endothelium and organized by the growth of fibrous tissue during the healing stage. This process will inevitably lead to the formation of fibrous bosses and irregularities on the auricular surface of the cusps. It is not these vegetations with which we are concerned, but the repeated deposits of fibrin which occur after the acute phase is over. In a previous investigation, in which 250 mitral valves from routine necropsies were examined, I showed that 7% bore fibrin deposits on the surface (Magarey, 1949). Only a small number of valves in this series were stenotic, and as the deposits also occurred on normal valves they are not to be regarded as pathognomonic of the chronic stage of the rheumatic process. Further investigation, during which about 30 rheumatic valves were examined, has shown that fibrin deposition on the surface of the cusps is far more common on rheumatic than on non-rheumatic valves. In fact, instead of the 7% in non-rheumatic valves, the frequency of occurrence is nearer 70% in the rheumatic cases. It is possible that the deformities associated with the healing stage of acute rheumatic fever described above encourage deposits of fibrin on the surface, and this sequence of thrombus formation followed by organization may be repeated throughout life, thus explaining the slow development of mitral stenosis over a number of years.

When sections from chronic rheumatic valves are studied there is a good deal of evidence to support this view. It can be seen that the deposits of fibrin which are often present become covered by endothelium extending from the contiguous surface of the cusp, and that fibroblasts from the pre-existing tissue gradually replace the plaque of fibrin by a layer of firm fibrous tissue. Some sections of thickened valves show this process to have been recurrent, the deeper layers of fibrin being in a more advanced stage of organization than the superficial (Plate, Fig. 1). This repeated fibrin deposition followed by replacement with fibrous connective tissue leads not only to thickening of the cusps but also to gradual narrowing of the valve orifice by a silting-up process.

I have previously made another observation which supports this view. Lambl's excrescences, small tags of endothelium-covered fibro-elastic tissue, occur commonly on the auricular surface of normal mitral valves. They are primarily superficial structures, but in sections of thickened valves they are sometimes seen partly buried within the substance of the valve. Even when so buried they are still readily recognizable by their histological architecture (Fig. 2). This partial submergence is further proof of repeated depositions of fibrin in the neighbourhood, the ensuing organization of these layers of fibrin leading to the gradual burial of these structures beneath the surface of the cusps.

If the commissures between the valve cusps are examined in specimens of established mitral stenosis, in more than half of the cases adhesions are seen between the adjacent surface of the cusps. These adhesions are the result of fibrin clot formation on the endocardium of the valve followed by organization, and it has been possible to demonstrate all stages of this process during the examination of this series of about 30 stenotic valves (Figs. 3 and 4). The process, when often repeated, will lead to gradual constriction of the orifice of the valve, and thus to the further development of stenosis. This opinion is contrary to that of Coombs. He states that organization of adhesions does not contribute to the approximation of the segments of the mitral valve at their ends, although he believes that fusion of the neighbouring parts of two cusps of the aortic valve may be due to this process.

The development of thickening of the valve and obliteration of the angles of junction of the cusps continues in the absence of any prolongation or recrudescence of the acute inflammatory stage of rheumatic valvulitis, and it can be demonstrated to be progressing years after there has been any history of acute manifestations of rheumatic fever. The slow but relentless development of mitral stenosis for many years after an attack of acute rheumatic fever can be thus explained.

## "Shortening" of the Chordae Tendineae

The same process of surface fibrin deposition followed by organization can account for the so-called "shortening" of the chordae tendineae and for the adhesions that form between them in chronic rheumatic

disease of the mitral valve. A gelatinous deposit of fibrin can sometimes be found adhering to the chordae tendineae, binding them together (Fig. 5). In this fibrin early organization may be present, and the end-results of this process are the formation of firm fibrous adhesions between the chordae. The same process taking place near the attachment of the chordae tendineae to the valve cusp will cause adhesions not only between the chordae themselves but also between them and the ventricular surface of the valve. In sections of some greatly thickened valves the chordae can be seen deeply buried in the substance of the cusp (Fig. 6). This condition could scarcely occur by any means other than organization of repeated surface deposits which eventually causes the various structures to become enveloped in a continuous fibrous covering. The fusion of the valvular attachment of the chordae tendineae to the back of the cusp will give the appearance of shortening and will at least accentuate any real shortening of the chordae which may occur by any other means. It will also greatly contribute to the rigidity and immobility of the cusps and thus to the stenosis.

### Conclusion

The conception of the pathogenesis of mitral stenosis which I have described has an added interest in view of the findings at operations undertaken for the direct surgical relief of the condition such as described by Baker, Brock, and Campbell (1950). The technique they favour is that of digital dilatation of the valve, the result of such procedure being a splitting of the stenosed valve along the line of the pre-existing commissures. This is the site where one would expect the tissues to give way had the commissures become occluded by fibrous adhesions as already described, and if, as is suggested, this is one of the main causes of the stenosis, relief would be expected from this operation. Glover, Bailey, and O'Neill (1950) describe the use of a specially designed knife to cut the commissures. Apart from those in the addendum their series consists of 50 cases, but the longest post-operative follow-up is only two years. It remains to be seen for how long the stenosis is alleviated by these manipulations. If the above conception of the process of the disease is correct, it is to be expected that the lesion may recur because the irregular surface of the cusps will still predispose to repeated thrombus formation.

### Summary

Evidence is produced to show that the long-continued progression of stenosis in rheumatic mitral disease is due, at least in part, to organization of repeated deposits of fibrin on the surface of the valve and in the commissures between the cusps.

In view of this mode of progression it seems that mitral stenosis relieved by digital dilatation and splitting, as recently described, may be expected to recur.

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# USE OF GALLAMINE TRIETHIODIDE (FLAXEDIL) IN MODIFYING E.C.T.

## A COMPARISON WITH D-TUBOCURARINE CHLORIDE AND DECAMETHONIUM IODIDE

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Since the introduction of convulsion treatment for the psychoses in 1934 by Meduna, the technique of administration and the indications for its use have undergone progressive modification. The main steps have been the development by Cerletti and Bini in 1938 of electrical methods of provoking a convulsion, the extension of the treatment to out-patients, and the use of curare and other drugs to reduce the severity of the muscular contractions during the convulsion.

### D-Tubocurarine Chloride

With the unmodified technique, still probably employed as a routine in most hospitals and clinics, and despite the use of some method of physical restraint, the incidence of fractures remains appreciable. Hobson and Prescott (1947), in their report on the use of D-tubocurarine chloride, showed that with an unmodified technique the incidence of crush fractures of the dorsal vertebrae remains at about 4%, but other writers have reported higher figures. Although it is agreed that these particular fractures have little clinical importance, and rarely lead to any lasting disability, they are of medico-legal importance, and other injuries are less innocent clinically. We do not yet know for certain that these vertebral fractures will not in fact lead to an arthritis some years hence. Although Thorpe (1948) seems to be satisfied with his unmodified technique, and reports no complications or fractures in the course of 3,000 convulsions, this is hardly the experience of the majority of those who carry out that treatment.

Until the introduction of curare as a means of modification there were always patients whose psychiatric condition demanded convulsion treatment, but who had to be denied it because their physical condition absolutely precluded its use. Shepherd and Watt (1949) reported a series of 50 patients successfully given electric convulsion treatment modified by D-tubocurarine chloride who would have been untreatable owing to physical disease had some method of modifying the convulsion not been employed.

The injection of curare and drugs with a similar action in a conscious patient produces a terrifying sensation (Hobson and Prescott, 1947; Davies and Lewis, 1949; Guild, 1950), and in practice such injections are therefore combined with a simultaneous injection of thiopentone. E.C.T. has long been criticized because in a fair proportion of patients it produces a dread that is severe enough to cause some to refuse further treatment; Cooper (1948), Thorpe (1948), and many others have used thiopentone by itself to diminish this fear. The use of thiopentone with a curarizing agent has this

advantage, and, in addition, it leads to a smoother, less restless recovery period than is often experienced after unmodified E.C.T.

D-Tubocurarine chloride, however, has not escaped criticism. Both Sandison (1947) and McGuinness (1947) have regarded it as being unnecessary and as having dangers of its own. Deaths from its use have been reported, chiefly from respiratory paralysis: Ulett *et al.* (1950) referred to six deaths in E.C.T. with curare. It has histamine-like actions, and produces bronchospasm in a small proportion of people (Hobson and Prescott, 1949); patients show a considerable variability in their response to it, and Gray and Halton (1948) reported cases of hypersensitivity; the period of recovery from E.C.T. is longer after curare has been used.

### Decamethonium Iodide

When Paton and Zaimis (1948) and Organe, Paton, and Zaimis (1949) published their reports on a new synthetic curarizing agent, decamethonium iodide (C10), it seemed that this drug might well prove to have advantages over D-tubocurarine chloride in modifying E.C.T. Davies and Lewis (1949), in an experimental and clinical study, reported that C10 was in fact preferable because in equivalent doses it spared the diaphragm more than did curare, it was free from disagreeable histamine-like side-effects, it was miscible with thiopentone, and it was cheap. Hobson and Prescott (1949) carried out a careful comparison of D-tubocurarine chloride and C10 in 40 patients undergoing E.C.T., and found that C10 had all the advantages of curare without its unpleasant side-effects, that it was more transient in its action, and that, being synthetic, it would not require biological standardization. Vetten and Nicholson (1950) reported that the recovery period from 15 mg. of D-tubocurarine chloride was 40 to 50% longer than from 3 mg. of C10.

Although C10 has continued to be used without any serious difficulty in modifying E.C.T., Gray (1950) abandoned its use in anaesthetic practice because of unpleasant experiences. Vetten and Nicholson (1950) reported one case of grave post-operative respiratory depression after a moderate dose of C10 in consequence of which they have abandoned its use in upper-abdominal surgery. The absence of any safe and effective antidote to it, and the dangers of the recommended antidote, pentamethonium iodide, with its liability to produce an alarming fall in blood pressure, have also led to uneasiness.

Ulett *et al.* (1950) employed the dimethyl ether of D-tubocurarine chloride for modifying E.C.T., and they prefer it to D-tubocurarine chloride. They found that, like the earlier drug, it has a tendency to produce laryngospasm and, occasionally, respiratory difficulty. They also record occasional general muscular weakness lasting 30 minutes to several hours after the shock.

### Gallamine Triethiodide

Another synthetic drug with a curare-like action—tri(diethylaminoethoxy)benzene triethyliodide (gallamine triethiodide—"flaxedil")—has also received attention since its introduction by French workers in 1946. Mushin *et al.* (1949) found it to be an effective curarizing agent, stable, easily prepared, miscible with thiopentone, antagonized by neostigmine, and devoid of side-reactions. The duration of action was slightly less than that of D-tubocurarine chloride. Doughty (1950) found gallamine triethiodide to be the most useful curarizing agent in facilitating laryngeal intubation, and Ruddell (1950), in a report on its use in 400 cases of general anaesthesia, stated that it was superior to D-tubocurarine chloride as a relaxant.

The only report we have so far seen on the use of gallamine triethiodide in E.C.T. is that of Presland and Palmer (1950). Their view is that for this purpose it is superior to D-tubocurarine chloride and to C10, and they point to the following advantages over one or other of its rivals: it is miscible with thiopentone; it has no histamine-like activity; it has an effective antidote: recovery from it is more speedy; and it spares respiration more than the other two drugs. This last observation is in direct contradiction to the opinion of Davison (1950), who found that with C10 the duration of respiratory depression was shorter than that of abdominal relaxation, and that the total duration of action was shorter than that of gallamine triethiodide.

The main complaint against gallamine triethiodide is that it produces a rise in pulse rate, but this does not seem to be of much importance in E.C.T. Many patients awaiting this treatment already have tachycardia owing to apprehension. Presland and Palmer state that the only contraindications to its use seem to be myasthenia gravis, asthma, and renal disease. Fairley (1950) reported the occurrence of prolonged intercostal paralysis after the administration of gallamine triethiodide to a woman with impaired renal function. This paralysis did respond, however, to the injection of neostigmine, but it must not be forgotten that deaths have been reported following the administration of neostigmine to patients in poor physical condition (Macintosh, 1949; Clutton-Brock, 1949).

### The Investigation

In nine months since February, 1950, 110 patients received a course of E.C.T. at the out-patient clinic of this hospital. In the early months, while D-tubocurarine chloride was being used, we employed this relaxant only if there were definite indications (physical disease or robust physique) that the severity of the convulsion ought to be modified; if there was none, the treatment was given unmodified, or, in patients who displayed apprehension, after an injection of thiopentone and atropine. In the later months, after C10 had been adopted, and subsequently gallamine triethiodide, we used these drugs on almost every patient, unless there was some contra-indication. The details are set out in Table I.

TABLE I

| Injection | No. of Treatments |
|---|---|
| None | 93 |
| Thiopentone, atropine | 73 |
| D-Tubocurarine, thiopentone, and atropine | 112 |
| C10, thiopentone, and atropine | 155 |
| Gallamine triethiodide, thiopentone, and atropine | 168 |
| Total | 601 |

It has been possible to form a clinical impression of the merits of the three relaxant drugs and to compare their efficacy, drawbacks, and dangers. The standard dose of atropine used was 1/100 gr. (0.65 mg) and thiopentone 0.25 g., but the amount of thiopentone given was increased or reduced as experience dictated in individual cases. The usual doses of the three relaxants

employed were: D-tubocurarine chloride, 15 mg.; C10, 3 mg.; and gallamine, 60–80 mg.; but here again the age, physique, and weight of the patient were taken into account in assessing the most suitable initial dose, and this was altered on a later occasion in the light of experience. An airway was inserted towards the end of the modified convulsion and an oxygen insufflator used in every case in which a muscle relaxant had been given.

*Dosage and Technique.*—All three preparations are issued in convenient amounts of solution, so that the dose can be accurately measured. The preparation of D-tubocurarine chloride employed was not miscible with thiopentone and atropine. This entailed the use of two syringes and the risk of the needle slipping out of the vein during the change of syringe. The other two drugs can be given mixed with thiopentone and atropine in a single syringe. The mixed solution of the three drugs was given rapidly, in 10 to 15 seconds, producing a full thiopentone effect in approximately 30 seconds.

### Rapidity of Effect

The maximum effect with D-tubocurarine chloride and C10 is in the fourth minute after injection. With gallamine triethiodide, the maximum effect is achieved in the second minute. This still leaves time after the injection to clean the patient's temples, and to adjust the headband before the maximum effect is reached. The rapidity of action of gallamine triethiodide has important advantages. (1) Less thiopentone is needed. We twice had the experience with one patient that the effect of a small dose of thiopentone wore off before the fourth minute, and he cried out, "I can't breathe." A larger dose was given on subsequent occasions, but it is desirable to keep the dose of thiopentone at a minimum for out-patients. (2) There is a saving of two minutes in each treatment. This may seem trivial, but it means that, under out-patient conditions, in each hour six patients can be treated with gallamine triethiodide, and only four with D-tubocurarine chloride or C10. Since we have been using gallamine triethiodide our waiting-list for E.C.T. has vanished, and we have never had to insert an airway and give oxygen because of cyanosis developing *before* the shock.

### Effect on Convulsion

In general the aim with physically healthy patients has been to modify the convulsion rather than to abolish it. In these patients the main risk of E.C.T. is in producing crush fractures of dorsal vertebrae owing to the violence of the initial "jerk" of spinal flexion. We have therefore attempted to give only enough curarizing agent to diminish this "jerk," so that with the assistance of mild physical restraint—a hard pillow under the dorsal spine and some pressure on the pelvis and shoulders to keep the spine from flexing—any tendency to spinal flexion was kept within very narrow limits. We were of the opinion that any attempt to abolish the convulsion completely in all patients was unjustifiable, as it exposed them to rather more hazards from full curarization than from leaving the convulsion to occur unmodified.

In physically handicapped patients we have aimed at a greater degree of modification, approaching complete abolition of convulsive movements in some of them. These patients have included two with mitral stenosis, one old man with auricular fibrillation, one with healed pulmonary tuberculosis, two with diabetes mellitus, one with Parkinsonism, one with asthma, one seven-months pregnant woman, several with varying degrees of hypertension, and many frail and aged people. The three curarizing agents are all capable of producing a high degree of relaxation and virtual abolition of the convulsion, but even with full curarization the various stages of the "convulsion" are still recognizable.

### Effect on Respiration

We can confirm Davies and Lewis's (1949) observation that, with doses that are equally successful in modifying the convulsion, C10 produces less respiratory depression than D-tubocurarine chloride, and they found that artificially assisted respiration had to continue for a shorter time after the convulsion. There is disagreement over the merits of gallamine triethiodide in this respect. Davison (1950) favoured C10 as an adjuvant in general anaesthesia because the total duration of action is shorter than that of gallamine triethiodide and because the duration of respiratory depression is shorter than that of abdominal relaxation. Presland and Palmer (1950), however, state that gallamine triethiodide used with E.C.T. spared respiration more than either C10 or D-tubocurarine chloride.

Our experience supports that of Presland and Palmer. Recovery of breathing is extremely quick after even a fully modifying dose of gallamine triethiodide. Often the inability to breathe covered only the physiological period of apnoea which accompanies and succeeds the epileptiform convulsion, and in many cases the use of an airway and insufflation with oxygen was routine rather than necessary. It may well be that E.C.T. itself cuts short the period of respiratory depression after gallamine, as has been reported with D-tubocurarine chloride (Hobson and Prescott, 1947; Scurr, 1949), but not with C10.

Assisted respiration was most necessary with D-tubocurarine chloride, and neostigmine was given on two occasions. No patient in this series developed bronchospasm. On three occasions after the use of D-tubocurarine chloride respiration became inadequate in the recovery room, and readministration of oxygen was necessary. With C10, respiration had to be assisted more often and for longer than with gallamine triethiodide, but no case gave rise to any alarm, and there was no indication for using C5.

### Other Factors

*Antidote.*—Neostigmine is an effective antidote to D-tubocurarine chloride and to gallamine triethiodide, but so far no safe and reliable antidote to C10 has been found.

*Recovery.*—This is without doubt quickest with gallamine triethiodide and most tardy with D-tubocurarine chloride. When curare was used some patients did not feel sufficiently recovered to leave hospital before 90 minutes after the injection. Almost all those who had gallamine triethiodide were able to drink a cup of tea within 20 minutes, and to leave the hospital less than 50 minutes after the injection and convulsion. C10 is intermediate in this respect.

*Cost.*—Each injection of D-tubocurarine chloride costs about three shillings; with C10 and gallamine triethiodide the cost is about ninepence.

*Complications.*—No physical complications have been encountered in this series, either in the patients who had modified convulsions or in those whose convulsions were

unmodified. Several complained of transient memory loss and impairment of concentration, and one became hypomanic; but these are complications of E.C.T., whether modified or not.

The nursing staff's opinion is quite clearly in favour of gallamine triethiodide and least favourable to D-tubocurarine chloride.

### Discussion and Conclusions

E.C.T. is a highly successful form of treatment for many depressive illnesses. In its unmodified form it has certain risks, and, moreover, it cannot be administered to many patients who require it, because they happen to be suffering from physical disorders. A minority of patients also find it exceedingly unpleasant. The use of D-tubocurarine chloride, coupled with thiopentone, overcomes these drawbacks to a very considerable extent, but modification with this drug entails several risks, which many experienced people feel should restrict its use to those suffering from serious physical disorders. The introduction of C10 as a muscle relaxant has proved in some hands to be an agent so free from hazards that in some clinics it is thought that the faint risks of not using it in an uncomplicated case now outweigh the slight risk of using it in every case.

As a result of considerable experience with gallamine triethiodide in the past few months we are of the opinion that this relaxant has certain distinct advantages over C10, and that the time has now arrived for using it in combination with thiopentone and atropine in every case, unless there is some contraindication. Now that gallamine triethiodide is available, we hold the view that the use of D-tubocurarine chloride for modifying the convulsion of E.C.T. should be abandoned. None of these drugs should on any account be employed unless a means of ventilating the patient through an adequate airway with oxygen is at hand.

So far few adverse accounts of gallamine triethiodide have been reported, and no trouble whatever has been encountered in using it in our series of patients. It should not be employed in myasthenia, it should be used with caution in cases of impaired renal function, and it is probably wiser on theoretical grounds to use C10 in asthmatics.

The conclusions of this comparison are roughly expressed in summary form in Table II.

TABLE II.—*Comparison of the Virtues of Three Relaxants in Modifying E.C.T.*

| Advantage | D-Tubocurarine (112 Treatments) | C10 (155 Treatments) | Gallamine Triethiodide (168 Treatments) |
|---|---|---|---|
| Miscible with thiopentone | 0 | + | + |
| Rapidity of effect .. | 0 | 0 | + |
| Relative absence of respiratory depression | 0 | + | + or ++ |
| Rapidity of recovery .. | 0 | + | ++ |
| Absence of side-effects .. | 0 | + | + |
| Antidote satisfactory .. | + | 0 | + |
| Cheapness .. .. | 0 | + | + |

We wish to thank Dr. Henry Wilson for his interest, and Dr. D. V. Martin and Dr. W. J. B. Rogers, who administered half the treatments with which this paper is concerned.

ADDENDUM.—Since this paper was completed we have carried out 256 treatments on 39 patients, using gallamine triethiodide, thiopentone, and atropine. This further experience has not led us to alter our views.

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## GALLAMINE TRIETHIODIDE AS AN ADJUNCT TO ELECTROPLEXY

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It is now accepted that curarization of a patient undergoing electroplexy for the treatment of mental disorder is a useful adjunct in avoiding traumatic complications, as it reduces the muscular force of electrically induced convulsions (Hobson and Prescott, 1947, 1949; Shepherd and Watt, 1949; Davis and Lewis, 1949). It has been established that tri-(diethylaminoethoxy)-benzene triethyliodide (gallamine triethiodide—"flaxedil") exerts a true muscle relaxant action, inhibiting the transmission of nervous impulses by acetylcholine and blocking transmission across the myoneural junction of voluntary muscle (Bovet *et al.*, 1947; Huguenard, 1948; Mushin *et al.*, 1949). The relaxant action is easily reversed by neostigmine or physostigmine (Wien, 1948). Wilson and Gordon (1949), while using gallamine triethiodide as a curarizing agent in anaesthesia for a series of 80 patients (20 adults and 60 children) undergoing surgical operations in the abdomen and in the chest, concluded that this drug produced adequate muscular relaxation and that it seemed to be devoid of undesirable side-actions. Other workers have had similar good results whilst using gallamine triethiodide in general anaesthesia (Ruddell, 1950; Doughty, 1950; Harrison, 1950).

It seemed to us that gallamine triethiodide might be of use in patients who required electroplexy with modification because of certain physical abnormalities. Twelve patients (two men, ten women) were selected who were thought to be suitable for convulsant

therapy and for whom there were physical contra-indications to its use. Three patients were suffering from severe rheumatoid arthritis, one had recent tendon sutures across the wrists following a suicidal attempt, and the remainder were suffering from hypertension and arteriosclerosis. Their ages ranged from 40 to 73 years.

## Method

In the morning, with the patients fasting, 1/100 gr. (0.65 mg.) of atropine sulphate was given to each of them 45 minutes before starting treatment. In every individual the first injection of gallamine triethiodide was given alone. It was our intention at the outset to give ten patients gallamine triethiodide alone for all treatments prior to the E.C.T. and then later to give ten other patients gallamine triethiodide plus thiopentone sodium and endeavour to make comparisons. But they so disliked the sensation of a feeling of suffocation with gallamine triethiodide alone that we decided after the first few injections to give all subsequent injections in combination with thiopentone sodium. For the first injection, or in some cases the first few injections, gallamine triethiodide was given as follows: 50 mg. was injected quickly, and an additional amount to a total of 60 to 100 mg. was given slowly during the next few minutes. We observed the relaxant effect of the drug by asking the patient to grip the hand, flex the feet, lift the leg off the bed, and raise the head from the pillow. When we had judged that sufficient relaxation was obtained we ceased injecting and noted the amount given. Subsequently this dosage was then given quickly at the next treatment. The dosage required varies from case to case, and must be calculated individually. We observed that once a satisfactory dosage was found this same amount produced sufficient relaxation at each subsequent injection.

Observations were made of the following: (1) the power to flex the fingers, by asking the patient to grip the observer's hand; (2) the power to raise the legs from the bed against the resistance of the observer's hand; (3) the power to raise the head from the pillow —the observer placed his hand on the patient's forehead and pressed downwards; (4) the plantar reflex, tested to demonstrate reflex activity; (5) blood pressure; (6) pulse rate; and (7) respiration rate.

## Results

In doses of 60–100 mg. intravenously, with the subject conscious, complete paralysis of the flexor muscles of the forearm and the flexor muscles of the foot and leg developed within three to five minutes. The facial, orbital, ocular, and laryngeal muscles were affected early, in two to three minutes, as evidenced by flickering of the eyelids, development of ptosis, difficulty in articulation, and slurring of speech. One patient said that she had gone blind, but on retracting her eyelids she could see, though vision was double.

The neck muscles were affected early and the patients were unable to raise the head. The muscles of the jaw were relaxed and the chin needed support. The small muscles of the hand, tested by grip, remained fairly strong until just before the paralysis of the intercostal muscles, when they weakened.

Complete relaxation of the abdominal muscles occurred in about three minutes. When all the muscles were in a state of relaxation, stroking the sole of the foot did not elicit the plantar reflex.

In two patients the paralysis induced by gallamine triethiodide was very soon neutralized by the injection of 1 mg. of neostigmine in each case. Full muscular power was regained in 10–15 minutes in these two patients.

We noted that when gallamine triethiodide was having its maximum effect the respiration increased in rate, often more than doubling its initial resting rate. Respiration became very shallow. The patient became distressed owing to the dyspnoea, and a rise in blood pressure occurred. The patient also became slightly cyanosed, but the administration of oxygen during this period did not produce any change in the blood pressure, nor did it add materially to the patient's comfort. When gallamine triethiodide was given alone it was found that a rise of at least 10 mm. Hg in systolic and diastolic blood pressure occurred (see Table). Often the rise was noted to be as much as 40 to 50 mm. Hg. We found, however, that when 0.25 g. of thiopentone sodium in 5 ml. of sterile water was given before the gallamine triethiodide was administered no vasopressor or depressor effects were caused by the subsequent injection of the drug (see Table). This suggests that the rise in blood pressure noted after gallamine triethiodide alone was due to the apprehension and distress caused by the giving of the injection and later by the paralysing effect of the drug, which made breathing difficult.

In most of the cases the blood pressure immediately after the convulsion was found to be lower when thiopentone sodium and gallamine triethiodide had been administered than when the latter alone had been given. Within 10–20 minutes after the fit the blood pressure and pulse rate had returned to resting normal in three cases in which the drug was given alone and in three cases in which it was given with thiopentone sodium. In all cases, after each injection of gallamine

*Blood-pressure Recordings Before and After Intravenous Injections of Gallamine Triethiodide Alone and in Combination with Thiopentone Sodium*

| | Case 1 (66 yr.) | Case 2 (53 yr.) | Case 3 (66 yr.) | Case 4 (51 yr.) | Case 5 (57 yr.) | Case 6 (49 yr.) | Case 7 (58 yr.) | Case 8 (71 yr.) | Case 9 (63 yr.) | Case 10 (48 yr.) |
|---|---|---|---|---|---|---|---|---|---|---|
| Gallamine triethiodide | 70 mg. | 80 mg. | 70 mg. | 70 mg. | 80 mg. | 80 mg. | 100 mg. | 70 mg. | 75 mg. | 60 mg. |
| B.P. before G.T. | 140/80 | 145/90 | 200/100 | 130/80 | 220/110 | 150/90 | 190/110 | 190/110 | 160/100 | 170/90 |
| B.P. 1 min. after G.T. | 150/90 | 150/100 | 240/130 | 140/90 | 240/120 | 160/100 | 240/120 | 190/120 | 200/120 | 180/100 |
| B.P. 1 min. after E.C.T. | 180/100 | 190/105 | 230/110 | 150/100 | 260/140 | 180/110 | 180/100 | 200/150 | 215/120 | 200/110 |
| B.P. 20 min. after E.C.T. | 140/80 | 140/90 | 190/90 | 130/80 | 230/110 | 150/90 | 190/110 | 190/110 | 190/120 | 170/80 |
| Thiopentone sodium | 0.25 g. | 0.25 g. | 0.25 g. | 0.25 g. | 0.25 g. | 0 25 g. | 0.25 g. | 0.25 g. | 0 25 g | 0 25 g. |
| B.P. before T.S. | 130/80 | 150/90 | 200/100 | 130/80 | 225/110 | 150/90 | 190/110 | 190/100 | 160/100 | 170/90 |
| B.P. 1 min. after T.S. | 140/90 | 160/100 | 170/90 | 140/80 | 145/80 | 110/80 | 120/80 | 110/95 | 130/90 | 150/80 |
| Gallamine triethiodide | 70 mg. | 80 mg. | 70 mg. | 70 mg. | 80 mg. | 80 mg. | 100 mg. | 70 mg. | 75 mg. | 60 mg. |
| B.P. 1 min. after G.T. | 130/80 | 140/90 | 170/90 | 130/80 | 140/80 | 110/75 | 120/80 | 110/95 | 130/90 | 150/80 |
| B.P. 1 min. after E.C.T. | 150/90 | 140/80 | 180/100 | 140/90 | 160/100 | 150/90 | 150/90 | 150/100 | 150/90 | 160/90 |
| B.P. 20 min. after E.C.T. | 148/80 | 140/90 | 190/100 | 130/80 | 200/100 | 110/90 | 150/90 | 190/110 | 180/110 | 170/90 |

triethiodide the paralysing effects of the drug had completely disappeared at the end of 20 minutes. No difference in the disappearance of paralysing effects was noted between those cases given the drug alone and those who received it in combination with thiopentone sodium.

### Description of Fit

When we had judged that sufficient relaxation and paralysis had occurred—usually within three to four minutes—a shock was given.

A fit was judged to be good by the flickering of orbicular and labial musculature; the arms and legs could be freely moved during the time the patient was in the "tonic" stage of the convulsion. In a somewhat less satisfactory fit the flexion of arms and legs could be easily overcome. On a few occasions apnoea was a little prolonged and the patient became cyanosed; oxygen and slight manual assistance to breathing soon overcame this, and natural respiration quickly returned.

### Toxic Effects

No bronchospasm occurred after over 90 injections of this drug. There was no marked sweating, and on only one occasion did we see pallor. Slight areas of erythema with weal formation were noticed around the site of injection on several occasions, and twice a fleeting erythema occurred over face and chest. It is of interest to note that one patient who had been receiving E.C.T. with D-tubocurarine before gallamine triethiodide was introduced presented an extensive rash on face and chest and a large urticarial weal with an area of erythema 4 in. (10 cm.) in diameter around the site of injection on each occasion, but on changing to gallamine triethiodide only a very small weal with an area of erythema ½ in. (1.25 cm.) in diameter occurred at the site of injection, and there was no generalized rash. This difference in reaction may be explained by the greater tendency of the natural product to cause histamine release. The use of gallamine triethiodide had no adverse effects on kidney function or blood picture in those cases tested

### Conclusions and Summary

Gallamine triethiodide ("flaxedil") was given to two men and ten women suffering from various physical conditions (hypertension, severe rheumatoid arthritis) and about to undergo electric convulsion treatment.

Dosage was determined in each case by studying the loss of power of various muscle groups: the neck muscles failed first, the hand grip relaxed just before the onset of intercostal paralysis.

After the induced fits, which were in no way impaired, recovery was rapid and complete within 20–30 minutes of the full dose.

The drug produced no fall in blood pressure, and there seemed to be fewer side-effects than with D-tubocurarine. A mild cyanosis from temporary apnoea occurred in several cases.

In two patients paralysis from gallamine triethiodide was completely abolished in 10–15 minutes by the injection of 1 mg. neostigmine.

Our thanks are due to Dr. A. G. Duncan, physician superintendent, Severalls Hospital, for his interest in this work and for permission to publish; to Dr. Charles Milne, registrar, who treated the two male patients, for his clinical notes on the cases; to Dr. Robert Forgan, medical consultant of May & Baker Ltd., for his information about flaxedil and also his helpful criticisms and suggestions; to Messrs. May & Baker Ltd., who furnished us with the flaxedil used in the investigation; and to Sister Corken and Nurse Nixon, who helped in the treatments.

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## STERNAL MARROW CULTURES IN TYPHOID FEVER

BY

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AND

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The only absolute proof that a patient is suffering from typhoid fever is the isolation of the organism. The widespread use of prophylactic injections of typhoid vaccine has to some extent lessened the value of *Salm. typhi* H and O agglutination. For this reason any method which will increase the number of cases yielding positive cultures should be explored.

The use of sternal marrow puncture for the detection of the organism has been stressed by several workers (Gerbasi, 1939; Ling *et al.*, 1940; Piaggio Blanco *et al.*, 1942). Gerbasi claims credit for the first systematic study of typhoid infection in children by examination of the bone marrow. He later used the method successfully in adults. He states that sternal marrow cultures often remain positive throughout the course of the illness even when other tests are negative. The bacillus may or may not appear in the blood during the initial febrile period, but it is a constant finding in the bone marrow, disappearing during the advanced stage of the disease or during recovery. He believes that the organism becomes fixed in the bone marrow and appears in the blood only in recurrent and temporary "spurts."

During a recent outbreak of typhoid fever at Evaton, Transvaal, 40 Bantu patients were admitted to Baragwanath Hospital under our care. We had, therefore, an excellent opportunity of testing these observations.

### Methods

In order that there should be no doubt about the diagnosis in these cases, no case has been included which did not conform to one or more of the following criteria: (1) a positive blood culture; (2) a positive sternal marrow culture; (3) a urine or stool specimen containing typhoid bacilli; (4) a post-mortem examination

with findings considered pathognomonic of typhoid infection; and (5) a significant or rising agglutinin titre with clinical features suggestive of typhoid fever.

H agglutination to a titre of 1 in 100 or O agglutination to a titre of 1 in 200, or both, have been used as minimum diagnostic titres. These titres conform to the minimum diagnostic titres suggested by Lewin (1938) for use on the Witwatersrand.

In order to isolate the organism from the bloodstream, blood was withdrawn by venepuncture and immediately inoculated into ox bile and nutrient broth. Simultaneously, sternal marrow puncture was performed according to the usual standard technique (Wintrobe, 1942) and the blood thus obtained inoculated into ox bile.

### Results

Sternal marrow puncture was performed on 28 patients. (Those under the age of 10 were not subjected to sternal puncture, although no valid contraindication exists against this diagnostic method in this age group, provided they are adequately sedated.)

A positive marrow culture was obtained from 18 cases (64.3%). In five of the 28 (17.9%) the marrow culture was positive when blood culture, done simultaneously, was negative. Twenty-one patients (52.5%) yielded positive blood cultures during some stage of their illness. In no instance was blood culture alone positive.

These results are lower than those quoted in the literature, but it is possible that with a greater number of examinations of the marrow on individual cases and on a larger number of patients a greater percentage of positive results would have been attained. Ling *et al.* (1940) performed marrow cultures on 38 patients suffering from typhoid and paratyphoid fever. Of 110 marrow cultures and an equal number of blood cultures done simultaneously on the 38 patients, there were 44 instances in which marrow culture produced the organism while blood culture was negative, and only twice was blood culture alone positive. Piaggio Blanco *et al.* (1942) isolated *Salm. typhi* from the marrow in 42 (93.3%) of 45 cases, while in only 27 (60%) was a positive culture obtained by examination of the blood.

### Summary and Conclusions

The value of sternal marrow culture in the diagnosis of typhoid fever is stressed. Positive cultures were obtained from 18 out of 28 cases. In five instances marrow culture was positive when blood culture, performed simultaneously, was negative. In no instance was blood culture alone positive.

It is suggested that sternal marrow puncture be more extensively used in the diagnosis of typhoid and paratyphoid infections.

We are grateful to Dr. J. C. Gilroy and Dr. A. D. Gillanders for their helpful criticism.

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# Medical Memoranda

## Some Cases of Poliomyelitis in a Country Practice

It is a common belief that one case of poliomyelitis, or, as I suppose, of paralytic poliomyelitis, is not followed by another in the same household. Another prevalent opinion is that the motor loss is at a maximum when the paralysis appears. Recently I have had reason to relinquish both these cherished beliefs.

### Case Reports

On September 9, 1950, Mrs. A., a young married woman of 28, came to stay on holiday with her brother, Mr. B., who was a railway porter, 24 years old, with a young wife and child. The patient had been vomiting a little for several days, and on the evening of September 10 had a shivering attack and a headache. I visited her and found her temperature to be 102° F. (38.9° C.). She was a fortnight overdue with her period and so presumably in an early stage of pregnancy. The next day she still had headache and also a low backache, but only a mild pyrexia; and the day after that, on which she was not visited, felt so well that she went downstairs, but soon returned to bed as she had a queer feeling in her back reaching right up to her shoulders. That night she had a slight menstrual loss. When I saw her on September 13 the loss and backache might easily have been thought to be the premonitory signs of an early abortion, but I was surprised to find that her temperature had risen from its low level of 99° F. (37.2° C.) two days before, being now 100.5° F. (38.05° C.). My partner saw her next day, and, being unable to find the cause of the unaccounted pyrexia, treated her symptomatically with tab. codein. co. On September 15 I again called, and should have been told (as I was) that the veganin had done marvels and the patient was much better; but I happened to barge into the room and found the patient being supported by her husband upon a chamber-pot. He said he had to help her because she could not support herself.

On examination I found a weakening of the right quadratus femoris, the ankle-jerk absent on that side, and weakness of the muscles of the back. To get to the upright position she had to push herself up with her arms. Her respiratory movements, both costal and diaphragmatic, were quite good, although subsequently in the isolation hospital the paralysis spread to the arms and the diaphragm and there was some question of putting her in an artificial lung. However, she improved and was even getting some movement back, when, on September 23, she felt poorly again, was found to be pyrexial, and died from heart failure within a few hours, the virus having apparently flared up to paralyse the vagus centre.

On September 18 Mrs. B. developed a backache with pyrexia. She agreed to go to the isolation hospital, where a lumbar puncture was done. This being completely negative, she was sent home on September 21. That afternoon her year-old baby, who had been taken to his grandmother's home, was brought back to his parents; he was at once seen to have a left-sided Erb's palsy, and, when he was set to crawl, an obvious weakness of the left leg. According to the grandmother he had appeared to have nothing but a slight cold previously. I am happy to report that the paralysis in the child extended no further; but on September 30 Mr. B. retired to bed with a cold, and when I visited him on October 2 was found to have a paralysis of the left deltoid. He was sent to the isolation hospital,

where he gave no cause for anxiety until on the morning of October 4, when the paralysis had spread rapidly to involve both arms and the diaphragm. He was put in an artificial lung, but died in a few hours.

R. A. NASH, M.R.C.S., L.R.C.P.,
D.Obst.R.C.O.G.

## A Case of Drug Eruption Induced by Hexamethonium Bromide

Of the skin reactions caused by therapeutic agents those due to the intake of iodides and bromides have long been recognized and are of fairly common occurrence.

With the recent introduction of the hexamethonium halides as blocking agents of the autonomic ganglia as described by Paton and Zaimis (1948a, 1948b, 1949), Barlow and Ing (1948a, 1948b), and Balaban *et al.* (1949), and hence their application in medicine as therapeutic measures in hypertension (Turner, 1950; Campbell and Robertson, 1950) and peptic ulcer (Kay and Smith, 1950a, 1950b), cases of halide eruption were not entirely unexpected. So far as we can ascertain, this is the first of such cases to be described.

### Case Report

A housewife aged 45 was known to be a case of hypertension and was admitted to hospital on September 6, 1950, for further investigation. No cause was found for the hypertension, and it was labelled essential in type. She seemed a suitable subject for trial with hexamethonium

bromide. A test dose of 100 mg. by intramuscular injection was given on September 19, and this was followed by a satisfactory fall in both systolic and diastolic blood pressure without any toxic effects. It was decided to continue treatment with the usual oral method, and the dose was increased gradually until September 29, when she received 1 g. three times a day. This was considered to be her maintenance dose. On October 4 a few tiny papules, which had not been present previously, were noted on the left naso-labial region. These were thought to be ? rosaceal in type and were treated with calamine lotion. The eruption became no worse and the patient was discharged home on October 7, with instructions to continue the same dosage—that is, 1 g. three times a day. This she did until October 11, when she reported to hospital because of a sudden exacerbation of the rash on her face. The presence of discrete papulo-pustules together with a vegetative plaque (see photograph) left little doubt about the diagnosis, and this was readily confirmed by one of us (J. S.). The administration of the drug was stopped.

The total dosage of hexamethonium bromide up to the appearance of the papules was 34,600 mg. spaced over a period of 16 days. In all, the patient received 53,600 mg. over a period of 23 days.

The eruption cleared up perfectly within a few weeks of cessation of intake of the drug.

### Comment

In the treatment of hypertension it is now generally accepted that the intake of sodium by the patient should be restricted (Ucko, 1950). In this case no table salt was added by the patient to her diet, and foods with a high sodium content were avoided. This probably reduced the sodium content of her diet to approximately 3 g. a day.

As recommended by Ucko (1950) and others, drastic curtailment of the sodium (usually as sodium chloride) to below 0.5 g. a day is probably essential if hypertensive signs and symptoms are to be alleviated. It would appear that simultaneous administration of the bromide or iodide salts of hexamethonium with this severe curtailment of sodium intake would theoretically induce halide intoxication, as it is now established that the halides can replace each other in their linkage with sodium and potassium (Wile, Wright, and Smith, 1922).

It would seem, therefore, to be a wise precaution, when treating hypertension with hexamethonium bromide or iodide, not to limit sodium chloride intake to a low level.

We are indebted to Dr. Douglas K. Adams, in whose wards this patient was treated, for permission to publish this case and for his advice and criticism.

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# Reviews

## TEXTBOOK OF MEDICAL TREATMENT

*Medical Treatment. Principles and their Application.* Edited by Geoffrey Evans, M.D., F.R.C.P. (Pp. 1,398; 51 figures. £5 5s.) London: Butterworth and Co. (Publishers), Ltd. 1951.

This book has been prepared by Dr. Geoffrey Evans with the aid of over fifty collaborators, the great majority of whom are consulting physicians. It is arranged in the alphabetical order of categories of diseases, not the diseases themselves. Thus the sequence runs: Central nervous system, chest, children, dehydration, etc. This arrangement saves repetition and allows the discussion of general principles, which is one of the aims of the book. Even so, there are 1,400 pages of text and 66 of index, and the book costs five guineas. The index is efficient and the text is creditably up to date. Aureomycin and chloramphenicol are discussed, but not terramycin. Cortisone and A.C.T.H. are not indexed as such, but are mentioned under the heading of rheumatoid arthritis, where they are given a single page of text; this may be compared with five pages devoted to artificial fever. The long lapse of time between the writing of a manuscript and publication of a volume of this size is sufficient to account for the difference in emphasis. No common condition seems to have been omitted, and treatments recommended are orthodox and comprehensive. It is probably as good a book on treatment as can be bought at the present time. The literary style of most of the contributors is clear, and the book itself is beautifully printed and bound; it lies open at the chosen page like a good Bible.

It has, of course, certain faults which are common to all compendiums on treatment. Apart from the frequent impossibility of separating treatment from diagnosis, which accounts for much of the length of the book, it is doubtful if it is wise or economical to include all facets of treatment in one volume, for they change at such a different rate, and a fault in one makes the whole construction out of date. The management and pastoral care of patients, psychotherapy, and dietetics alter relatively slowly. On the other hand, treatment with drugs and physical agents is at present advancing, as it were, on a conveyer belt which needs frequent editions of books to keep pace with it. In matters like social care, diets, and availability of new drugs great differences exist between the U.S.A. and England, which makes it difficult for books to cross the frontiers and recoup the cost of frequent editions.

As regards special criticism, having turned to the book for help in some recent problems, I have not found it as discriminating as the book by Dunlop, Davidson, and McNee. Under the heading of migraine we are told that if water retention is suspected 30 gr. of urea should be given; as the normal adult excretes 30 g. of urea daily it is hard to see what effect such a small dose could have. The recent influenza epidemic has brought many of us face to face with the problems of emphysema, which is at all times a common disorder, particularly in industrial areas. A book which deals with principles of treatment should discuss the advances which have been made in recent years in the assessment of disability and the effects of treatment in emphysema. It should explain what is meant by high-output failure of the heart, the accumulation of $CO_2$ in the blood, and the rise in cerebrospinal fluid pressure. These points are omitted, inhalation of adrenaline or *iso*-propyl-adrenaline is not mentioned, and the difficult decisions concerned with the use of oxygen, digitalis, venesection, and sedation are too briefly discussed under the heading of pulmonary heart failure.

There are too many *ex cathedra* pronouncements for a book of this size and cost. Admittedly it is possible to rely too much on the literature and the use of scissors and paste, but the fact remains that readers nowadays expect references and data in support of claims for treatment. Under sarcoidosis one is told bluntly that hilar and pulmonary lesions do not respond to calciferol; experts, however, regard the question as still under judgment. The book recommends treating tabes dorsalis with penicillin, plus courses of intramuscular bismuth and intravenous arsenic, the latter to be repeated yearly for two to four years, and fever therapy to be used if the spinal fluid shows a paretic curve. It is also suggested that a Herxheimer reaction can be avoided by giving small doses of penicillin for the first 24 hours. Most of this would be effective treatment, but the reader should be warned that ideas are changing rapidly in this field, and that, apart from the desirability of treating tabes with penicillin, all these recommendations are controversial and unsupported by statistics. Of pancreatic cysts it is said that "because of the lack of inflammation they are often easy to excise"; this does not tally with my own small experience of pancreatic cysts nor with my reading of textbooks of surgery.

Perhaps I have been unlucky in the sections I have consulted—I do not pretend to have read the book through. To avoid the charge of carping criticism, let me add that some of the sections are admirable, such as those on psychiatry, psychoneurosis, and rehabilitation. The real question is whether it is possible to-day for fifty collaborators to write a book on medical treatment which is uniformly scientific and satisfying, and which is inexpensive enough to outweigh the fact that much of it is out of date before it is published. The problem is perhaps better dealt with by the Year Books and by separate monographs.

L. J. WITTS.

## HISTORY OF MALARIA

*The Conquest of Malaria.* By Dr. Jaime Jaramillo-Arango. (Pp. 125; 36 plates. £1 1s.) London: William Heinemann Medical Books. 1950.

The author of this well-illustrated and very readable book discusses three important chapters in the history of malaria. In Section I he describes in an interesting way early views of the nature of malaria, the discovery of malarial pigment, of the parasite, and eventually of the mosquito cycle, and the result this last discovery has had upon methods of prevention. As a short, balanced, and informed statement of the facts this section could scarcely be improved upon. In the third section, too, he gives a well-informed account of research relating to the isolation of the alkaloids of cinchona and successive discoveries of the antimalarial drugs "plasmochin," "atebrin," and still later compounds including "paludrine."

It is, however, in the second section—on the early history of cinchona—that the author's chief contribution is made. Eminently familiar with the locality whence cinchona first came and with access to the early literature

such as few could hope to have gained, he provides in this section the latest authoritative work on this interesting chapter in the history of medicine. Besides facsimile reproductions of many passages in early writings, the plates illustrating the book include portraits of Laveran, Golgi, Marchiafava, Manson, Ross, Grassi, Celli, as also of Beauperthuy, Finlay, and Lazear, pioneers in yellow-fever work of Caventou, and of Pelletier, the first to isolate the alkaloid quinine, of Woodward and of Doering, who synthesized quinine, and of Curd, Davey, and Rose, the discoverers of paludrine, as well as a photograph giving a general view of Loja, the town on which early stories of cinchona centre, and one of the country in the district of La Paz whence came *Cinchona calisaya*, the source of all modern varieties of cinchona. The book will appeal to those desiring a short, readable account of research in malaria and to the student of medical history interested in the early literature dealing with cinchona.

S. R. CHRISTOPHERS.

## TREATMENT OF DIABETES

*Therapie des Diabetes Mellitus.* By Dr. Georg R. Constam. (Pp. 291; 16 figures. 16.50 francs.) Basle: Benno Schwabe and Co. 1950.

Three years ago the author produced an admirable manual for diabetic patients which was perhaps too detailed for them and insufficiently so for doctors. In his new book every aspect of treatment is closely detailed, and the result is the most useful book that has appeared in the German language on the treatment of diabetes. The chapters are logically arranged, dealing first with metabolic theory, with the diagnosis of glycosurias, with clinical manifestations, and very fully with diet and insulin. The author gives ample space to discussing the many complications which affect so many systems, from the toes to the eyes.

The book contains enough detailed technical matter to enable the doctor to make his own solutions for tests of the urine and blood, and it is interesting to note that the Nylander and other Continental tests have been replaced by the usual ones used in Britain and America. A good feature of the book is an excellent bibliography at the end of every chapter. There are a few first-class illustrations of insulin injection technique, and the colour chart of urine is the best we have seen anywhere. The book is well printed and produced, and ought to become a classic in German-speaking countries.

R. D. LAWRENCE.

## A DOCTOR'S LIFE

*Memories of Eighty Years.* By James B. Herrick, M.D. (Pp. 270. £1 17s. 6d.) Chicago: University Press. London: Cambridge University Press. 1950.

This record of an unusually long, active, and happy life has much in it which should appeal to doctors everywhere, though it has a special interest for those who have grown up with Chicago. After a strenuous career as general practitioner, teacher, and consulting physician, Dr. Herrick achieved national fame as a cardiologist, and became, as he says, "willy-nilly a specialist." All through his professional life he has had what may fairly be described as a passion for diagnosis, and he paid many visits to Europe to work under eminent physicians, whom he describes very frankly and always with humour. In 1904 he published a small handbook of medical diagnosis, which he says "so filled the long-felt want that no second edition was ever called for." It was in 1912 that he laid the foundation of his claim to recognition as a cardiologist by reading a paper on "Clinical Features of Sudden Obstruction of the Coronary Arteries" before the Association of American Physicians. It was based "on a case of coronary thrombosis in which I had made an ante-mortem diagnosis." The paper aroused no attention, but Herrick persevered, and in 1918 he says that coronary thrombosis came into its own, and he received full recognition from the profession.

The book is full of strong common sense and is very readable. Dr. Herrick has met many of the famous doctors of his time and has interesting and often amusing stories about them. The only adverse criticism I have to make about a book I have enjoyed is that it might have been better had it been shorter. There is a certain amount of repetition in it which could have been avoided.

ALFRED COX.

## BOOKS RECEIVED

*Review is not precluded by notice here of books recently received*

*Physical Diagnosis.* By R. H. Major, M.D. 4th ed. (Pp. 446. 32s. 6d.) London: W. B. Saunders. 1951.

*A Textbook of X-Ray Diagnosis.* Edited by S. Cochrane Shanks, M.D., F.R.C.P., F.F.R., and P. Kerley, M.D., F.R.C.P., F.F.R., D.M.R.E. Vol. 1. 2nd ed. (Pp. 434. 45s.) London: H. K. Lewis. 1951.

*Modern Trends in Neurology.* Edited by A. Feiling, B.A., M.D., F.R.C.P. (Pp. 717. 63s.) London: Butterworth. 1951.

*British Surgical Practice Index.* Edited by Sir Ernest Rock Carling, F.R.C.S., F.R.C.P., and Sir James Paterson Ross, K.C.V.O., M.S., F.R.C.S. (Pp. 363. 20s.) London: Butterworth. 1951.

*Hermann and Dorothea: an Epic.* By J. W. von Goethe. Translated into English verse by G. F Timpson. (Pp. 80. 7s. 6d.) London: The Mitre Press. 1951.

*What is the Prana of Yoga?* By E. S. Shrapnell-Smith, C.B.E., F.C.S., M.I.Chem.E. (Pp. 36. 2s. 6d.) London: L. N. Fowler. 1951.

*Trends in Psycho-Analysis.* By Dr. M. Brierley. (Pp. 320. 21s.) London: Hogarth Press. 1951.

*The Microkaryocytes.* By K. G. Khorozian, A.B., M.S., M.D. (Pp. 969. $12.) Boston: Meador Publishing Company. 1951.

*Nobel: The Man and His Prizes.* By H. Schück and others. (Pp. 620. Kr. 48 or 65, according to binding.) Stockholm: Sohlmans Förlag. 1950.

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Polyglot medical dictionaries are still relatively uncommon. All those whose task it is to read European medical literature will welcome the appearance of *Medizinisches Wörterbuch: Dictionnaire Médical* (Medical Dictionary) (Berne: Hans Huber. London: H. K. Lewis and Co. £6 6s. 1950), prepared by Swiss specialists under the direction of Dr. E. Veillon. The dictionary is arranged in three sections: German, English, French; English, French, German; French, German, English. Each section contains over 30,000 medical terms; those relating to the natural sciences rather than to clinical medicine have been ruthlessly pruned. American spelling has been adopted in the English section, and the well-known medical dictionary of Dorland has been taken as a standard. When the English word given may appear somewhat obscure, its meaning more elaborately defined will always be found in "Dorland." Although this is a relatively expensive work, it does take the place of three separate dictionaries, and on that account should be convenient to use.

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## MEDICAL AUXILIARIES AND NATIONAL REGISTRATION

The training and qualifications of the large body of persons who offered their services in auxiliary capacities in medicine began to occupy the serious attention of the British Medical Association and other bodies more than 20 years ago. In 1933 the Representative Body approved the establishment of a national register of such persons, and in 1936 the Board of Registration of Medical Auxiliaries was incorporated. The board has done pioneer work of great value in ensuring authoritative guidance for hospitals, public bodies, and individual practitioners concerning the credentials of the persons so employed. But the board is a voluntary organization and naturally has had to depend upon the extent to which the professional associations in each of the branches of the auxiliary service could encourage or stimulate their members to seek registration. With the advent of the National Health Service the question of a statutory register of those actually employed in the service takes a new importance.

Two years ago eight small committees, each charged with a different branch of the auxiliary services, were set up by the Government to consider the questions of supply and demand and training and qualifications, and their report, which has just been issued, is summarized on another page. The chairman of all eight committees was Mr. Zachary Cope, and a happier choice could not have been made; but even Mr. Cope, with his persuasiveness and ability to reconcile different points of view, can hardly have expected unanimity among people who, though all comprised under the generic term "medical auxiliaries," profess widely different skills, undergo widely different training, and work under widely different conditions. The medical man may think of the auxiliaries as a homogeneous body of persons who are there to assist him, very much in the same way as the members of the nursing profession. But the 12,000 persons now employed in these various capacities in the National Health Service may look at the matter differently. They range from almoners and dietitians in hospitals to chiropodists and speech therapists, whose work is largely outside hospitals, and from physiotherapists and remedial gymnasts to radiographers and laboratory technicians. The members of the Institute of Medical Laboratory Technology, for example, who number over 4,000, may be connected with hospitals, or with the blood transfusion service, or with the public health laboratory service, or with the pathological departments of universities, or with laboratories in industrial concerns; they may be serving in some capacity in connexion with the diagnosis and treatment of disease in individual patients, with the prevention and control of epidemic disease, with the production of sera and vaccines, or with teaching and research in pathology. The Chartered Society of Physiotherapy has over 17,000 members, who practise in various fields—massage, electrotherapy, hydrotherapy, and so on. The Society of Radiographers has more than 3,500 members, and some of them are connected with the diagnostic, some with the therapeutic, and some with the side of the pure physicist.

Some of these highly skilled workers, quite understandably, resent the term "auxiliary," which suggests inferiority of status. The work of many of them calls for training which is not wholly acquired at the feet of medicine. The almoner, for example, is trained in social service. The occupational therapist and the radiographer are trained in crafts and skills which may be outside the purview of the medical man under whose supervision they work. Sometimes the distinctions between different branches of the auxiliary services are not appreciated. The physiotherapists, for example, suggested a registration council which would embrace occupational therapists, remedial gymnasts, and themselves, for occupational therapy might be considered as a continuation of physiotherapy in the process of rehabilitation. But the occupational therapists pointed out that to set up such a council would unduly emphasize the physical side of their work, whereas occupational therapy has its more considerable psychological aspects; it is said that more than half the work is done in mental hospitals.

The main report of the Cope Committees recommends for the whole body of auxiliaries a single council to administer a system of statutory registration for the National Health Service. Each branch

of auxiliaries would have its separate register which would be open to all those qualified for that service, whether already employed in it or not. The council would be assisted by a series of professional committees, each concerned with a single service and composed of experts in that field. Under this new machinery, schools, courses, and examinations would be recognized, the relation of supply and demand over the whole range of auxiliary services would be studied, joint consultation and co-ordination of training would be provided for, and it would be ensured that methods of training kept pace with advance in medical thought and practice. Guidance could be given on the demarcation of functions as between one type of medical auxiliary and another, and as there is every reason to suppose that new branches of medical auxiliary work will arise these could be recognized in the National Health Service as might be appropriate.

Some of the medical auxiliaries may cavil at the proposed composition of the council. Of its 21 members only six would be medical auxiliaries, unless, of course, the Privy Council or the Ministry of Health appointed such persons as its representatives. The character of the council would be predominantly medical. But numbers in this connexion are probably not important, and the main work would be done in the professional committees, where a majority of auxiliary membership would be provided. There remains the work of the professional associations, which have hitherto with great success maintained a high standard of training and qualification in their respective spheres. The eight committees report in every case that the work of the principal associations is adequate and satisfactory. These bodies under the new proposals will be shorn of some of their responsibilities. The recognition of schools and the like would pass to the council. On the other hand, the council would not itself undertake training courses and examinations. Moreover, many of the professional associations have members working outside the National Health Service in private practice and may wish to maintain in addition their own registers. There is some safeguard in a general council, which is less likely than a branch council to interfere with details of training. Nothing is said in the report on the subject of discipline, which is an important function of bodies concerned with education and registration in medicine, architecture, and law, on which this proposed council is patterned. Many matters remain to be thought out, but Mr. Zachary Cope and his 40 or more colleagues on the eight committees have done a statesmanlike piece of work in face of difficulties which, though not referred to, can be imagined.

## CIRRHOSIS AND FATTY INFILTRATION

Much has been written in recent years on the relationship of nutrition to liver disease. Experiments on rats, dogs, and other laboratory animals have conclusively shown that diets deficient in lipotropic factors lead to the accumulation in the liver of large quantities of fat, often exceeding 30% of its wet weight. Moreover, the persistence of the dietary deficiency and the resultant fatty infiltration of the liver lead to the progressive fibrosis of the organ, culminating in a condition virtually indistinguishable from Laennec's cirrhosis. A second type of cirrhosis has also been produced experimentally, and independently of fatty infiltration: this is distinguished from the first by its coarse nodular structure and irregular fibrosis, and was found to result from healing of massive necroses induced by diets deficient in the thio-amino acids.[1] Whenever a pathological state of uncertain aetiology in humans is reproduced in animals the question inevitably arises about what relation, if any, exists between the method used to produce the experimental lesion and the naturally occurring disease in man. Since both varieties of cirrhosis apparently also occur in man, the relation of the human disease to nutrition becomes a problem of outstanding interest. There is an inevitable tendency, however, to extend the experimental results to the sphere of human pathology, and to erect an aetiological edifice greater than is perhaps warranted by the foundation of experimental fact. It is therefore salutary that Professor J. H. Dible, in his Humphry Davy Rolleston lectures, published in the opening pages this week, has brought his considerable experience as experimentalist and morbid anatomist to bear on the problem of the relationship of fatty infiltration to hepatic cirrhosis and of the extent to which valid distinctions can be drawn between the different types of fibrosis of the liver in man.

A study of the fat content of 150 consecutive unselected livers at necropsy showed that only in three did the amount exceed 15%, which is the critical level according to Glynn, Himsworth, and Lindan[2] for the development of fibrosis. Moreover, in the rat this level must be maintained for 100–300 days for a well-developed cirrhosis to occur, which in proportion to the span of life is equivalent in man to 8–20 years. As Dible justifiably says, no condition is known in man in which such excessive quantities of fat are found in the liver for such periods of time. Finally, of 69 cases of portal cirrhosis, only 30 showed microscopic evidence of increased fat. Dible therefore concludes that "in the cirrhotic liver of man there is a lack of pathological evidence which would permit us

to presume that this condition is a late effect of prolonged and heavy fatty infiltration." On the basis of the material available some may think that this conclusion tends towards the dogmatic rather than the proved. With the quite low incidence of portal cirrhosis in this country—1.66%, according to Dible's own necropsy figures—it would hardly be expected that amounts of fat in the liver exceeding 15% would occur in more than the 2% of cases in which they were in fact found. It is, moreover, unjustifiable to conclude from the difference in life span of species that the time taken for pathological processes to develop is longer or shorter in the same proportion. There is, for example, no evidence that the healing of a skin incision, which in man takes about a week, is accomplished in the rat in eight hours. Nor is there any reason to suppose that human liver cells deprived of their oxygen supply can survive 25 times as long as rat liver cells in similar circumstances. On the contrary, it is probable that the human cells would prove more susceptible to oxygen deprivation. Finally, with regard to the absence of excessive amounts of fat in cirrhotic livers, almost all the investigators[2-4] of dietetically induced fatty cirrhosis have emphasized the progressive decrease in the fat content of the liver with the progress of the cirrhosis, the amount often being no more than normal in fully developed cases.

In 1911 Mallory drew attention to the heterogeneous nature of hepatic cirrhosis and distinguished particularly between the diffusely fibrotic, finely granular liver of Laennec's cirrhosis, the aetiology of which was obscure, and the coarsely nodular, coarsely fibrotic liver, the nodular hyperplasia of Marchand, often associated with a history of exposure to some hepatic poison. Since that date most pathologists have agreed with Mallory's conclusions, but have observed a number of cases which did not fall typically into either group. This is hardly surprising, since the underlying disease process of both types of lesion may be chronic and progressive, and the final picture the result of necrosis, fibrosis, and regeneration. Great importance is usually placed upon the size of the individual hepatic nodules in the differential diagnosis, but it must be emphasized that this can be quite misleading, since regeneration nodules in Laennec's cirrhosis of long standing may reach 1 or even 2 cm. in diameter, and progressive fibrosis in cases of nodular hyperplasia may break down the originally large nodules into fine granules. Therefore, though these two kinds of cirrhosis may be easily distinguished in their extreme phases, time may bring their progressive approximation till differentiation may become impossible. This apparent similarity of end-result, however, does not justify denial of a fundamental difference of origin.

Part of the confusion between the two types of cirrhosis undoubtedly results from misuse of the terms monolobular and multilobular. They are usually applied to the naked-eye appearance of the liver, in which case they are synonymous with the terms "finely" and "coarsely granular" respectively and, as already mentioned, can give no unequivocal indication of the type of cirrhosis present. If, however, the term multilobular be restricted to those cirrhoses in which individual nodules can be seen microscopically to be composed of several more or less intact liver lobules, then there can be no doubt that the condition has arisen as a result of a partial massive necrosis or so-called subacute yellow atrophy. A serious attempt was recently made in the U.S.A. to establish criteria to distinguish the Laennec from the post-necrotic type of cirrhosis. Samples of 106 cirrhotic livers were reported upon independently by eight of the country's leading pathologists, and a surprising degree of agreement was reached, although no generally accepted criteria of differentiation had been previously agreed. In consequence Goldblatt[5] was able to conclude that "there is but little doubt that the classical examples of Laennec's and of post-necrotic cirrhosis are distinct entities and easily distinguished."

The study of infective hepatitis and its sequelae by Dible and others has shown that lesions ranging from centrilobular zonal necrosis to extensive massive necrosis may occur in the acute phase, and from slight portal cirrhosis to typical post-necrotic scarring and nodular hyperplasia in the later stages. Since either type of cirrhosis may thus occur after infective hepatitis, it might be concluded with Dible that no valid or useful distinction can be drawn between them. But surely this would be no more justifiable than a refusal to distinguish between glomerulo-nephritis and hypertensive nephrosclerosis merely because lesions of the latter may result from a chronic attack of the former. Acute and subacute yellow atrophy arising as a complication of virus hepatitis is undoubtedly conditioned by factors other than the virulence of the causative agent, although this may play a part. Among these factors, nutritional status is undoubtedly of importance. The finding that necrosis occurs most commonly in the left

1 Himsworth, H. P., and Glynn, L. E., *Clin. Sci.*, 1944, **5**, 93.
2 *Brit. J. exp. Path.*, 1948, **29**, 1.
3 Chaikoff, I. L., Eichorn, K. B., Connor, C. L., and Entenman, C., *Amer. J. Path.*, 1943, **19**, 9.
4 Blumberg, H., and Grady, H. G., *Arch. Path.*, 1942, **34**, 1035.
5 *Liver Injury*, 1947, Trans. of 6th Conference, Josiah Macey, Jun. Foundation.
6 Lucke, B., *Amer. J. Path.*, 1944, **20**, 471.
7 Gillman, J., and Gillman, T., *Arch. Path.*, 1945, **40**, 239.
8 Waterlow, J. C., *Spec. Rep. Ser. med. Res. Coun., Lond.*, 1948, No. 263.

half of the liver strongly supports this contention.[1 6] The diffuse fibrosis that may follow infective hepatitis thus becomes comparable with that which may follow the repeated action of any liver poison causing zonal necrosis, while the acute and subacute atrophy and consequent post-necrotic scarring may be regarded as a manifestation of an entirely different phenomenon, possibly a conditioned nutritional deficiency.

Professor Dible makes a very strong case for showing that at Hammersmith the vast majority of cases of cirrhosis are not the result of nutritional defect. Many have probably developed out of occult or non-icteric hepatitis. It may well be true that in this country generally cirrhosis is mainly a late result of virus hepatitis. It would be unwise, however, to conclude that these findings are applicable to those areas of the world where nutritional standards are far below those of West London. In the West and East Indies, Africa, and in large areas of Asia the development of severe fatty infiltration of the liver of a degree comparable to that required to cause cirrhosis in experimental animals undoubtedly occurs. Moreover, the nutritional state originally responsible for the fatty liver can and does persist for periods of time more than adequate for the evolution of diffuse hepatic fibrosis. Such evolution has been repeatedly observed by serial biopsies and its prevention by adequate dietary supplements convincingly demonstrated.[7 8]

## CORTISONE AND TOXAEMIA OF PREGNANCY

As the facts about toxaemia of pregnancy accumulate, so, it seems, do the theories about the disease, for so far are we from a true understanding of the pathogenesis of the condition—or should it be conditions ?—that few writers have made serious attempts to reconcile the facts but rather have sought to postulate fresh hypotheses to explain their newly adduced evidence. Concepts embracing imbalance of hormones in the aetiology of toxaemia are not altogether recent ; the pioneer work of G. Van S. and O. W. Smith, who built up an elaborate structure involving the oestrogens, progesterone, and chorionic gonadotrophin, is now well known if not generally understood. With the shift in interest towards the adrenal cortex that has been so prominent of late it is not surprising that attempts have been made to implicate the hormones secreted by this gland in the deranged physiology of toxaemia. As usual, the evidence is conflicting, and, whereas that of some older investigations[1 2] suggested inadequate adrenocortical activity, more recent work seems to agree on an increased excretion of corticoids in the disease. Indeed, one theory, based on the finding of low 17-ketosteroids and high corticoids in toxaemia, seeks to ascribe the disease to this hormonal imbalance.[3] Tobian[4] has claimed to have found a high output of the mineral-controlling corticoids in toxaemia, and it is possible that the imbalance lies between these and the glucogenic corticoids.

In spite, therefore, of the absence of clear knowledge of the role of the adrenal cortex in toxaemia, and in face of the serious possibility that positive harm might result from the exhibition of cortisone (by reason of its salt- and water-retaining tendencies) Professor Henry Moore and his colleagues in Dublin, being fortunate in having access to a continuous supply of the drug, have thought it expedient to try it out in a series of eight cases. Their results are reported in detail in the present issue of the *Journal* (p. 841). It is quite clear that all their patients were seriously ill, with raised blood pressure, albuminuria, and, in five cases, oedema. Two had had convulsions before admission, and one had them during labour. In seven of the cases the indications on admission were for termination of the pregnancy (in the remaining case no hopes for foetal survival were entertained). Nevertheless cortisone treatment was continued for from 5 to 27 days, and seven live babies were delivered, of which two died from prematurity (one with an intracranial haemorrhage).

This record, as those well acquainted with the risk to the foetus of severe toxaemia will agree, is quite impressive, especially since the clinical improvement brought about by cortisone was marked in all cases. The need for sedatives was reduced, headache was relieved, diuresis seemed to be promoted, and oedema decreased—at least temporarily, though in some cases it was replaced or accompanied by ascites. In spite of this, blood pressure was essentially unaffected, and albuminuria was at best only moderately diminished. The ultimate results, so far as the mothers were concerned, are also interesting. Five of the patients left hospital apparently normal ; one later died of congestive heart failure ; one was left with serious cardiovascular renal disease requiring further attention ; and one developed schizophrenia five days after cessation of cortisone treatment. Though such psychotic reactions have been observed *during* treatment with cortisone or A.C.T.H., it seems probable that this was a puerperal psychosis not connected with cortisone treatment.

" In reporting the present eight cases of pregnancy toxaemia treated with cortisone we record facts " ;

1 Fauvet, E., *Klin. Wschr.*, 1936, **15**, 1356.
2 —— and Munzer, L., ibid., 1937, **16**, 675.
3 Devis, D., and Eeckhoudt, M. D. van, *J. clin. Endocrinol.*, 1949, **9**, 1436.
4 Ibid., 1949, **9**, 319.

so state the authors, and very wisely they refrain from drawing too much by way of conclusions. It is clear that the notable and, as judged by results in these cases, beneficial effects of cortisone were produced without very significantly modifying the underlying disease process, and they are a perfect illustration of the principles which Dr. J. S. L. Browne so ably enunciated in his Society for Endocrinology lecture at the Royal Society of Medicine on April 5 (reported on page 880). On Dr. Browne's iceberg analogy, cortisone seems to have melted away some of the underwater part of the disease and to have made some of the much smaller above-water part (the easily observed signs and symptoms) sink below the surface. The result was that all the patients seemed to respond well, though a good deal of the disease (the underwater portion) still remained. Nevertheless, since in toxaemia one is usually faced with an acute condition which generally resolves once the pregnancy has terminated, the cortisone umbrella may afford valuable protection to the patient until that natural resolution can be attained. Indeed, for both mother and baby it might even be life-saving.

## THE BUDGET AND THE HEALTH SERVICE

Budgets nowadays are unlikely to be popular, and the one this year is no exception. It imposes new and heavier burdens on nearly everyone, though it gives some relief to old-age pensioners and to parents with several children. The most striking feature of it is the proposal to charge people about half the cost of dentures and spectacles obtained under the National Health Service. There is no doubt that some such measure was overdue, for disquiet at the mounting cost of the Health Service has for long been felt both in Parliament and outside. But this measure must be an unpopular one, and the Government is to be commended for having had the political courage to introduce an arrangement that many of its own supporters and even the Opposition have feared to advocate. According to the Chancellor of the Exchequer, there will be no charge for children's spectacles, and expectant and nursing mothers will continue to receive free dental treatment; children will continue to receive free treatment in schools. Those for whom the charges mean hardship will receive payment in whole or in part from the National Assistance Board.

In his Budget speech Mr. Gaitskell made two significant statements on the cost of the Health Service. First is the fact that the estimate of the cost of the Service originally submitted to him for 1951–2 was about £30m. higher than in 1950–1. This increase, Mr. Gaitskell said, was due in the main to higher prospective expenditure on the hospital service. But, as was shown in an article in this *Journal*,[1] the actual increase has been kept down to about £5m. The intention, according to Mr. Gaitskell, is to set a ceiling of £400m. on the net cost of the Health Service to the taxpayer. He was careful to say that this ceiling is to remain "for the time being." In a period of rising prices, it is hardly to be expected that this financial limit can be maintained indefinitely. Mr. Gaitskell's other significant statement was that the introduction of the charge for half the cost of dentures and spectacles had been allowed for in the estimates for the Health Service that were presented to Parliament last month. The proposed charges explain the fall in the estimated cost of the dental service, and in particular the lower estimate for supplying and repairing glasses, while the estimate for sight-testing remained virtually unchanged. Apparently the Government considers that the demand for spectacles will continue at a high level. But it must be emphasized that the benefits to the finances of the Health Service that will be derived from the charges have already been used, for they have gone to pay for the increase in the cost of the hospital service that has been sanctioned for 1951–2.

New taxes especially burdensome on doctors are the increased purchase tax on new cars (from 33⅓ to 66⅔%) and the additional 4½d. on every gallon of petrol. Large sections of the community will suffer no direct hardship from them, for they can pass the cost on to the customer. Doctors in the Health Service cannot; though of necessity they use cars more than most people, they must find the additional expense from their own pockets. The profession would not wish to be more favoured than their fellow taxpayers, but they should not have to suffer a substantial disadvantage, and no doubt their representatives will take the matter up with the Government.

Negotiations on the general practitioners' remuneration were postponed until after this Budget and must be seen in the light of it. No one expected that the Chancellor would find an abundance of surplus money to be spent on the Health Service. In fact he has fixed a limit and imposed a charge so that the expenditure may lie within it. But, having taken the drastic step of imposing charges in order to sanction increased expenditure on hospitals, he can hardly

[1] *British Medical Journal*, 1951, 1, 754.

refuse to find money for a section of the profession that even the Government now seems to realize is underpaid. Mr. Gaitskell referred to the need to prevent any reduction in the standards of the "hospital, family doctor, and consultant services below what is really essential." The standards of general practice may be brought into danger if it continues to be financially unattractive.

## MENTAL DEFECTIVES IN INSTITUTIONS

The Mental Deficiency Acts (the principal Act was passed in 1913) have stood up well to the test of time. Only within the last few years has public opinion caught up with, and in some ways perhaps advanced beyond, the principles laid down in the Acts, and it is no secret that they are again under review and that much preliminary work has already been done. Such clauses as that concerned with the certification of "moral defectives" will probably be changed or even swept away altogether: one large institution in England has admitted no patient certified in this category for more than 20 years. Thus in advocating an inquiry into the Mental Deficiency Acts the National Council for Civil Liberties is to some extent preaching to the already converted.[1]

All doctors who certify patients under the Mental Deficiency or Lunacy Acts would agree that there must be no curtailment of the freedom of the individual unless essential for his own good or for the protection of the community. Unfortunately the National Council for Civil Liberties, in putting forward its views, relies too much on a one-sided account of a small number of cases and on such unsupported statements as "Five out of six cases [of certified defectives detained in institutions] arising at random sent for full and formal mental testing have proved to be not mentally defective." Many will take this to imply that five out of six defectives are incorrectly certified, and the main effect will probably be to cause unnecessary distress to the relatives of the many thousands of mental defectives in this country. What are the chances of wrongful certification? Under the N.H.S. Act the duty of ascertainment belongs to local health authorities. Some of these employ whole-time specialists; others use the services of hospital psychiatrists. But, though there are obvious advantages in employing only specialists to certify, many local authorities expect their own assistant medical officers to undertake this work. It is only right to say that these medical officers, who have all had a short postgraduate course in mental deficiency, gain from their experience in the field an exceptional understanding of the needs of defectives and of the problems of their relatives. Assuming, however, a patient has been wrongly certified by the first doctor examining him, what happens next? Another doctor (preferably the patient's family doctor) and a magistrate (sometimes a whole bench of magistrates) must also "wrongfully" certify the patient before he can be sent to an institution. The medical and legal commissioners of the Board of Control must agree to this "wrongful" certification. The patient then enters an institution (now under the aegis of a regional hospital board), where he is examined by a specialist, who certifies yet once more to the Board of Control that he is a defective. At the end of the first year of detention, and on later occasions, he is examined by a visiting panel of magistrates, who have an independent medical referee to advise them and who report to the Board of Control on the advisability of retention or discharge. At any time the patient or any relative may appeal to the Board of Control for release, and any letters sent to the staff of institutions must, by law, be forwarded to the Board of Control.

Besides suggesting that wrongful certification often takes place, the National Council for Civil Liberties is critical of the Board of Control. This is a panel of experts, legal and medical, with a lay chairman, which advises the Minister of Health on all matters pertaining to mental health. The Board acts as a court of appeal on all decisions made by the committees of management of institutions for mental defectives and can overrule all such decisions. Discharge from an institution may be granted by the visiting magistrates when a patient reaches the age of 21 years, but at all other times discharge is the prerogative of the Board of Control. Since the war the rate of discharge has been greatly accelerated. The Board of Control is non-political and non-partisan, and it seems fair to say that it is activated by one motive only: the interest of the patient.

The National Council for Civil Liberties makes the fantastic suggestion that high-grade defectives are wrongfully detained in institutions so that their labour may be exploited. Waiting-lists are enormous, and institutions already have many more patients than they were built to accommodate. Does the council seriously believe that there is a huge conspiracy of doctors, lawyers, magistrates, and members of management committees endeavouring "wrongfully" to keep patients in institutions, while all the time hundreds of letters are being received from frantic parents begging for their children to be admitted? It is the policy of all progressive management committees to develop the mind of each patient to its full capacity and by instruction and training to fit him or her for life in the community. Secondly, for those who will never be able to lead an independent existence the institution must provide as happy a home as possible. It would be too much to expect that the committees' decisions will always coincide with the opinion of the patient's relatives—especially those relatives whose interest in the defective becomes marked only when he begins to earn. But, all in all, there is little doubt that local authorities, management committees, and the Board of Control regard their heavy responsibilities with the greatest seriousness. Any improvements in the law which will ease their difficulties will be welcomed.

[1] *50,000 Outside the Law*. Published by the National Council for Civil Liberties, 46, Westbourne Grove, London, W.2.

## THE FOLIC ACID ANTAGONISTS

After more than three years' experience in the treatment of acute leukaemia with the folic acid antagonists, an assessment of the therapeutic value of these drugs should be possible. In 1949 Tiersch and Philips[1] estimated that about 250 cases had been treated and that temporary remission had followed in some 30%. It must be stressed that the remissions are never more than temporary, often incomplete, and seldom of more than a few weeks' duration. Cure has never been recorded. There is general agreement that improvement is more likely in children, less common in adolescents, and rare in adults; it is most frequent in the lymphoblastic form of the disease, less in the myeloblastic, and least in the monocytic. In brief, these drugs offer a child with acute lymphoblastic leukaemia a 25–30% chance of a few weeks' improvement, provided their administration is supported by blood transfusion and the antibiotics. During this short respite toxic reactions such as stomatitis, diarrhoea, vomiting, alopecia, and an enhanced liability to haemorrhage may replace the symptoms of leukaemia. There appears to be little difference in the action of the various members of the group: aminopterin has been used most extensively, but in last week's *Journal* Drs. J. V. Dacie, E. Dresner, D. L. Mollin, and J. C. White record their experiences with a-methopterin (4 - amino - N10 - methylpteroylglutamic acid) in seven cases. Their report makes depressing reading: a significant remission was obtained in only one patient, a child with acute lymphoblastic leukaemia. Toxic reactions were common, and the liability to haemorrhage was of particular frequency. In any disease less hopeless than acute leukaemia perseverance in the face of these results would scarcely be justified.

1 *Amer. J. med. Sci.*, 1949, **217**, 575.

## BAR SINISTER

When it comes to giving practical help to the illegitimate child and its mother even the welfare State has still to turn to the voluntary worker. The National Council for the Unmarried Mother and her Child was formed in 1918, and during its relatively short existence it has not only helped many thousands of individual mothers and children but also influenced the course of social progress. Among advances in the law for which the National Council can take some of the credit were the Legitimacy Act of 1926, which allowed children to be legitimized by the subsequent marriage of their parents, and the recent Adoption Act (1950). Since 1918 there have never been less than four illegitimate babies in every 100 live births (the highest percentage was 9.35 in 1945). The mortality among legitimate and illegitimate infants in 1918 was 91 and 186 respectively per 1,000 live births; in 1949 the figures were 32 and 45. A higher infant death rate is of course far from being the only disadvantage of illegitimacy, which often presents complicated social and legal problems to those who try to help unmarried mothers and their children. These workers, whether voluntary or professional, will find a small book[1] recently published by the National Council of the greatest practical value, for it is the first time all the legal provisions relating to illegitimacy have been plainly stated in one volume. Much other useful information, including some guarded remarks about paternity tests, is also included. As Professor Moncrieff writes in his introduction, "It is one thing to have these [social and medical] services available: it is another to make sure that they are intelligently used." By the publication of this book the National Council is doing its best to ensure that those who are in a position to help illegitimate children and their mothers should not be handicapped by lack of knowledge.

1 *Illegitimate Children and their Parents*, edited by Lena M. Jeger. Published by the National Council for the Unmarried Mother and her Child, 21, Coram St., London, W.C.1. Price 3s. net (3s. 6d. post free).

## WHAT MAKES A MUSCLE CONTRACT?

A correspondent, commenting on a recent answer in "Any Questions?" about acetylcholine and muscle contraction,[2] points out that acetylcholine is one link in a complex chain of events most of which are ill-known or unknown. Hence it would be misleading to imply that "the muscle action potential" acts directly on the contractile elements, for the final link between excitation and contraction is still missing. Its nature was considered at a discussion meeting at the Royal Society in 1949.[3] It seems certain that the last stage of the excitatory process is the momentary electrical depolarization of the surface of the muscle fibre. Something then travels inwards across its substance, acting as a trigger for the processes which result in the "active state" of muscle. This "something" is not a substance, for diffusion is far too slow; it must be an event of some kind—the propagated release, for example, of polarized particles normally held in line by the electrostatic charge on the surface.

The energy released by a muscle is made up of three independent quantities—"heat of activation," "heat of shortening," and "mechanical work." The first of these begins very early, and starts off at its maximum rate before visible shortening occurs. It is regarded as a sign of chemical processes accompanying the transformation of the resting to the active state. The earliest signs of this active state are increased optical transparency and decreased extensibility, both beginning so early as almost to run into the end of the electrical change accompanying excitation. The bridge across the gap is being extended from both ends: it may be possible to join it before long. Professor A. V. Hill discussed this problem in greater detail in the Sharpey-Schafer Memorial Lecture[4] which he gave in Edinburgh last February.

2 *British Medical Journaal*, 1951, 1, 652.

3 *Proc. roy. Soc. B*, 1949, **137**, 45.

4 *Rev. canad. Biol.*, in the press.

## *REFRESHER COURSE FOR GENERAL PRACTITIONERS*

# CORONARY ARTERY DISEASE—I. THE CLINICAL SYNDROMES

BY

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Sooner or later the hearts of most adults are affected by arteriosclerotic changes in the coronary arteries; fortunately, in only a minority are the obliterative changes so advanced as to impair seriously the myocardial blood supply and thus give rise to symptoms Myocardial ischaemia may be circumscribed or diffuse, temporary or permanent, acute or gradual in onset, depending on a number of factors. Hence, when blood flow is disturbed by obliterative disease in the coronary tree a variety of overlapping syndromes may result.

### Diagnosis of Coronary Sclerosis

The diagnosis of arteriosclerotic heart disease is based primarily on symptomatology. In contradistinction to other forms of heart disease, chest pain is a very characteristic feature. It dominates the clinical picture of coronary sclerosis.

In the absence of a history of pain the diagnosis of coronary sclerosis is less certain but may be presumed when heart failure in an acute or chronic form is encountered in the absence of other provoking cause. Cardiac asthma and acute pulmonary oedema should always suggest coronary disease as readily as the gradual development of congestive failure in an elderly person.

Disturbances of rhythm can give a clue to the diagnosis. A bout of auricular fibrillation may be the first evidence of arteriosclerotic heart disease. Curiously it is seldom associated with angina. Complete heart-block, for instance, with or without its characteristic syncopal attacks, has for its origin an arteriosclerotic basis more often than any other cause. Block of one or other bundle-branch is more common than block of the main stem of the bundle. Branch-block is not in itself a cause of symptoms, but it is a common manifestation of coronary damage.

Coronary sclerosis can be productive of symptoms without there being a change in the size of the heart. Except in the presence of congestive failure, radiological examination seldom shows more than minimal enlargement. It is worth emphasizing that coronary heart disease occurs independently of thickened radial, retinal, or other arteries, and that it is not a mere product of age. Youth does not exclude the diagnosis. The myocardial infarct is its hallmark.

As clinical examination may not elicit any physical signs, even in the presence of serious coronary disease, the diagnosis often depends on an assessment of symptoms. It is therefore imperative to hear the patient's own account of his difficulties and his personal description of their nature and development. This applies particularly to the differentiation of the causes of precordial pain.

### Angina Pectoris

The basis of cardiac pain is ischaemia, the result of a discrepancy between the oxygen supply and the oxygen needs of the myocardium. The quantity and quality of the blood delivered to the active muscle depend largely on the calibre of the vessels, the blood pressure, the heart rate, and the haemoglobin content. The demands of the heart for oxygen are determined primarily by the amount of work which it is called upon to perform. In health considerable reserves permit ready adjustments between the supply and demand, but in the presence of thickened and rigid coronary arteries with narrowing of their lumen the delivery of adequate amounts of blood falls short of the local metabolic needs. Pain is then apt to occur and to persist until either the debt is made good or local necrosis develops.

The quality of the discomfort varies greatly from patient to patient. Some deny that they have pain, and emphasize a sense of heat, weight, oppression or tightness in the chest, or a choking in the throat induced by exercise or emotion and equally promptly relieved by rest or peace of mind. Upward radiation of retrosternal pain, with numbness and tingling in the jaws and gums, or downward radiation of similar sensations in one or both arms to the elbows, wrists, and hands, are very characteristic features. Distress more readily provoked after than before a meal, and earlier in onset in cold than in warm surroundings, is commonly noted.

The "second-wind" phenomenon can be a misleading feature of organic coronary disease. The patient then observes that an attack, often quite severe, is readily provoked when exercise is first undertaken. Having rested a minute or two and recovered from the initial pain, he finds, on resuming his activities, that his capacity for effort thereafter quickly increases. He can walk at a similar or faster pace, perhaps for hours, with freedom from distress. It is commonly the first hole of a round of golf which presents the greatest difficulties to the anginal patient. A reactive hyperaemia, which makes good the initial coronary insufficiency and which is thereafter maintained by gentle exercise, has been advanced as the explanation for this common feature of coronary disease.

Accounts of other chest pains—arthritic, muscular or pleural, submammary and functional, peptic, biliary, or oesophageal in origin—can all be misleading, particularly when the patient is liable to two types of chest pain—the short-lived constrictive pain or transient ischaemia, and a more prolonged pectoral or upper abdominal ache, the product of fatigue, anxiety, or other cause. The dominant oppressive quality of genuine coronary pain, its wide radiations, and its precise relation to activity are its typical features. It is a good rule that if a man can take a brisk walk on a cold day without interruption necessitated by substernal pain he is not suffering from angina of effort. Occasionally, in those of less active habits, the pain is experienced only under conditions of emotional distress.

*Instrumental Proof.*—When doubt exists about the nature of the attacks an exercise test may be employed with advantage. A true anginal attack can usually be

induced within a few minutes by making the patient run up a flight of stairs, step up and down on a stool, or undertake standing-running exercise at as brisk a pace as he can manage; it can as promptly be relieved by rest on a couch. In a large proportion of sufferers from angina the electrocardiograms show, for a few minutes immediately after exercise vigorous enough to cause even minor distress, transient alterations in the pattern of the RST segment and T waves (see Fig. 1). This is

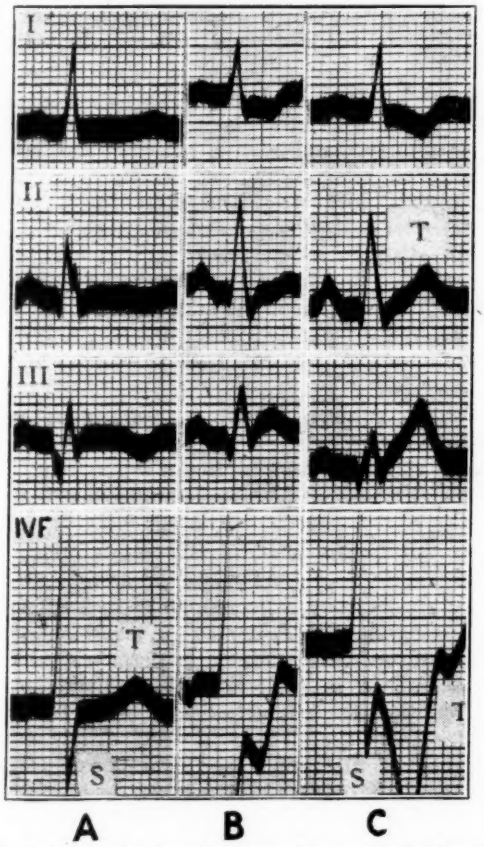


FIG. 1.—The attack of angina pectoris temporarily disturbs the pattern of the electrocardiogram in the majority of sufferers—a finding of value when the diagnosis is in doubt, as thereby the cardiac origin of the pain may be substantiated. Column A from above downwards records in each of the three standard limb leads and one chest lead (from the region of the apex beat) a single heart cycle under resting conditions. The patient, a man of 57, with a five-year history of angina, performed an exercise test sufficient to induce a mild attack of pain with well-marked dyspnoea. Column B presents similar leads from the same patient recorded consecutively from above downwards at intervals of a few seconds up to two minutes as he lay on a couch after completion of the test. The alteration of the form of the ST intervals, most evident in the chest lead (IVF), is evidence of ischaemia and confirms the cardiac origin of the pain. Column C shows that similar alterations in pattern present 5 to 6½ minutes after exercise in this man. More than 15 minutes elapsed after this induced anginal attack before the electrocardiograms regained the form existing before the exercise test was undertaken.

an important test of coronary efficiency, as in doubtful cases it may provide the only objective proof of the cardiac origin of the pain. Casual electrocardiograms recorded in the intervals between attacks may be of normal form or show only evidence of inert myocardial damage. They are of much less value than those displaying a resolving pattern of ischaemia in serial records after exercise. A simpler diagnostic method, but less reliable on account of the allowance which must be made for the "second-wind" phenomenon and for psychic influences, is the employment of nitroglycerin as a therapeutic test.

### Coronary Thrombosis with Myocardial Infarction

The features of the major attack of coronary thrombosis are well known. The formation of the circumscribed infarct commonly gives rise to prolonged substernal pain of great severity which persists for hours. Profound shock develops rapidly. Restlessness, pallor, sweating, nausea, and vomiting may be followed in severer cases by respiratory distress and signs of left ventricular failure with evidence of congestion along the margins of the lungs, in the axillae, and at the bases posteriorly. The blood pressure falls progressively for a few days.

Examination may show tachycardia, a feeble apical impulse, poor quality heart sounds, and a triple rhythm, and within a day or two local pericardial friction may occasionally clinch the diagnosis.

Tissue necrosis accounts for the prompt leucocytosis, early febrile reaction, long-sustained disturbance of the sedimentation rate—a sign which, persisting for a month or more, is often helpful in establishing the

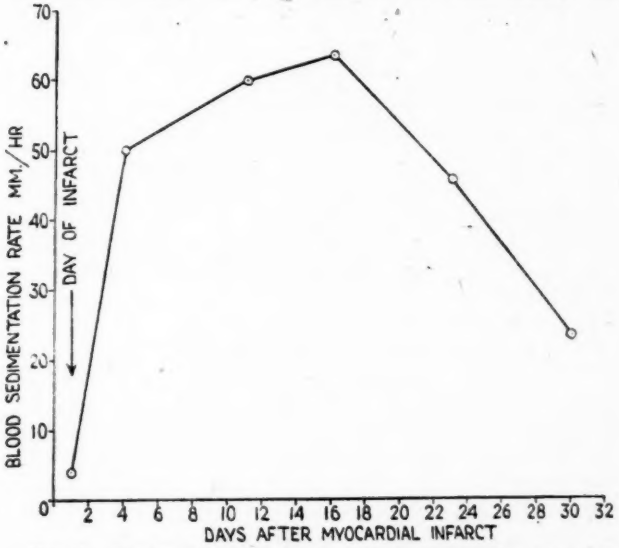


FIG. 2.—The sustained elevation of the sedimentation rate after a myocardial infarct is often a diagnostic sign of value. The disturbance is slow to develop, reaches a maximum in the second or third week, and reverts to the normal range within a month or two as a rule.

diagnosis in retrospect (Fig. 2)—and the sequence of changes observed in serial electrocardiograms. An increased clotting tendency of the blood, usually maximum at the end of the second week, explains the proneness of these patients to thrombo-embolic complications and the hazard of early death when the worst of the acute illness is apparently past.

Milder attacks of coronary thrombosis are common and are readily overlooked. In taking a history from a patient whose account suggests angina pectoris, inquiry should always be directed to the possibility of one or more attacks of infarction. A history of a minor occlusion, perhaps with acute symptoms of no more than 10 to 20 minutes' duration, may be obtained by having him describe his longest, his most severe, or any unexpected or unprovoked attack of pain. Suspicions will be strengthened by any admission of unusual exhaustion accompanying the attack or a less prompt restoration of bodily well-being thereafter.

*Instrumental Proof.*—The nature of the attack may be established by multiple-lead electrocardiograms,

which are capable of locating the site of the myocardial infarct with accuracy in most instances. By special techniques, using multiple chest and unipolar limb leads, anterior, antero-septal, antero-lateral, posterior, postero-lateral, high lateral, and certain septal infarcts, which would have escaped detection some years ago, can now be recognized and the diagnosis established even when months or years have elapsed since the acute episode. Exceptionally, even serial electrocardiograms repeated at intervals of a few days after the acute infarction fail to confirm the diagnosis. This is true particularly of certain septal infarcts. The method, like other laboratory procedures, therefore has its limitations, but refinements in technique are steadily reducing the likelihood of error.

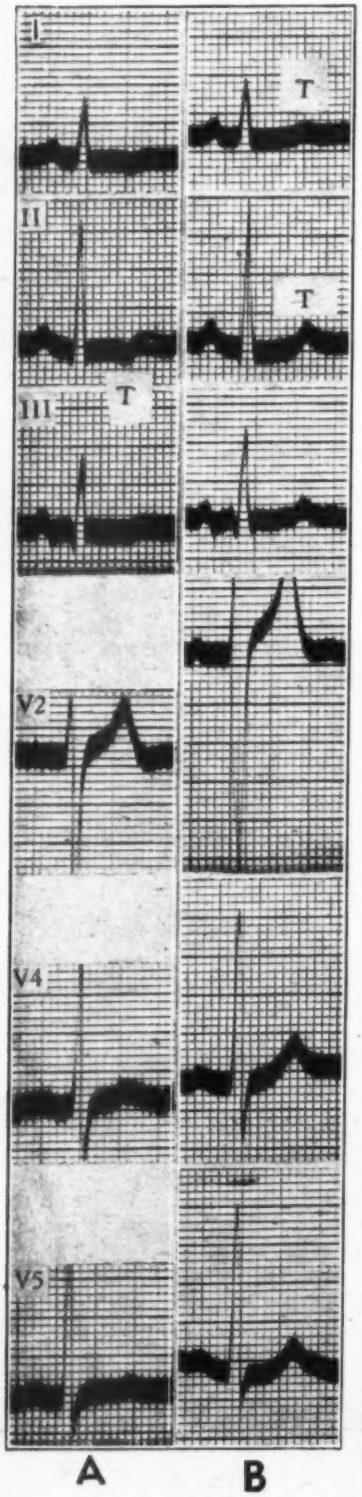


FIG. 3.—Coronary insufficiency produces a temporary disturbance in the electrocardiogram, the pattern reverting to normal within a day or two. Column A (taken on December 19) displays from above downwards electrocardiograms each of a single cardiac cycle in the three standard limb leads and in three chest leads. These were recorded 48 hours after the onset of a severe anginal attack of seven hours' duration, provoked by intense emotional distress but unaccompanied by shock or by signs of tissue necrosis. The patient was a man of 30, whose attack developed while under cross-examination by the police. He was admitted to hospital with probable coronary thrombosis. Column B (taken on December 22) presents similar electrocardiograms from the same patient after two further days in bed. The pattern has reverted to normal form. Comparison indicates that the inversion of the T waves in Leads I, II, and III present on the first occasion has been corrected and the T waves in chest Leads V2, V4, and V5 have increased in amplitude.

### Coronary Insufficiency

In a physiological sense all attacks of angina pectoris and the various grades of myocardial infarcts are examples of coronary insufficiency. In recent years this particular term has, however, been applied by Master and his colleagues to a fairly distinctive syndrome intermediate between the milder attack of infarction and the severer anginal seizure. Occasionally ischaemic attacks are asymptomatic, but more often they are characterized by spontaneous cardiac pain at rest, longer and severer than the usual attack of effort angina and yet not as severe as the clear-cut episode of coronary thrombosis. These attacks may proceed in the more prolonged instances to tissue asphyxia, with the development of a patchy speckled subendocardial necrosis evident in the papillary muscles or in the deepest muscular layers of the left ventricle. Coronary sclerosis, moderate to severe in degree, is the rule.

The attacks are not the result of coronary occlusion but develop under conditions of increased cardiac work, diminution of blood flow, or defective oxygenation of the blood. Hence, in the presence of coronary sclerosis, severe and prolonged physical exertion, intense emotional distress, a paroxysm of tachycardia, an exacerbation of hypertension, or, on the other hand, prolonged hypotension or the sudden anaemia of acute blood loss, as for instance a profuse haematemesis, may result in myocardial ischaemia severe enough to lead to tissue necrosis.

The most ominous of these attacks are those lengthening bouts of severe angina experienced at rest at increasingly shorter intervals for no apparent reason, so that ultimately a "status anginosus" may be described. Such a sequence often heralds a major coronary thrombosis with massive infarction.

*Instrumental Proof.*—As might be anticipated, acute coronary insufficiency is accompanied by depression of the S–T intervals with flattening or inversion of the T wave in two or more leads—a pattern very similar to that observed in induced attacks of angina. In the latter condition the characteristic deformities seldom persist for more than 15 to 20 minutes. In coronary insufficiency of the type now under consideration the ischaemic pattern wears off in hours or at most in a few days, its long persistence denoting diffuse subendocardial necrosis of some severity. In contrast, the electrocardiographic pattern of the circumscribed myocardial infarct of coronary thrombosis undergoes a more gradual transformation, the process commonly extending over months or years. An example of the electrocardiograms of coronary insufficiency is shown in Fig. 3.

### Other Syndromes of Coronary Sclerosis

The diagnosis of myocardial infarction is so important, and so many cases are missed on account of the absence of pain, that it should be a rule to consider this possibility under a variety of conditions. Among these, attacks of nocturnal dyspnoea are predominant. Every attack of cardiac asthma should be regarded as the product of a myocardial infarct unless other demonstrable cause exists. Similarly, a sudden pulmonary oedema, so characteristic of acute left ventricular failure, may mask other symptoms and be revealed only as the product of an infarct, when the subsequent behaviour of the blood pressure, the sedimentation rate, and serial electrocardiograms supplement the diagnosis.

Sudden prostration or collapse, syncopal attacks, or giddiness, with residual exhaustion and general weakness, are sometimes explicable on a similar basis. Less clear-cut syndromes occur in the elderly. Nocturnal

restlessness with insomnia and perhaps a minor sense of dyspnoea followed by a transient auricular fibrillation may provide a clue which would be otherwise missed were a search not made for evidence of tissue necrosis. The occurrence of systemic and commonly fatal embolism a week or two after the restless night too often clarifies the diagnosis when, alas, the opportunity for effective therapy is past.

Finally, there are those incipient cases of congestive heart failure of gradual onset in which by a process of exclusion the aetiology is assumed in the absence of other cause. The electrocardiogram may then provide a further link in the diagnostic chain.

## MEDICAL AUXILIARIES IN NATIONAL HEALTH SERVICE

### PROPOSED STATUTORY REGISTRATION

"Medical auxiliaries are persons who assist medical practitioners (otherwise than as nurses) in the investigation and treatment of disease by virtue of some special skill acquired through a recognized course of training." With this definition—which did not go unchallenged by some of the medical auxiliaries concerned—eight committees set up by the Minister of Health and the Secretary of State for Scotland have been considering the supply and demand, the training and qualifications, of certain of the classes of medical auxiliaries employed in the National Health Service—namely, almoners, chiropodists, dietitians, laboratory technicians, occupational therapists, physiotherapists and remedial gymnasts, radiographers, and speech therapists. Mr. V. Zachary Cope was chairman of all the eight committees, and one other medical and one lay member were common to them all. For the rest, each committee consisted of two or three—in one case four—medical members and usually two members representative of the category concerned. This eightfold report has just been published as a White Paper,[1] the first part being devoted to problems common to all these auxiliary services, and the second to the assessment of each service separately.

The committees, in the course of two years, have held more than 100 meetings and received a vast amount of evidence. Evidence from the British Medical Association and from the present Board of Registration of Medical Auxiliaries was tendered to all eight committees. Mr. Zachary Cope had a difficult team to drive, due, not to personalities, but to the diversity of the interests represented. The one common factor is that the auxiliaries (with the possible exception of the chiropodists) work under the direct or indirect supervision of a doctor. But in the various schemes of training the points of emphasis are different, and the desirable standards of attainment are not the same in all the categories. Certain basic sciences, such as anatomy and physiology, may be necessary in most cases, but obviously the radiographer and the physiotherapist require a much more comprehensive knowledge in this field than the chiropodist or the speech therapist. These latter two need to have a certain amount of detailed anatomical knowledge, but relating to two different parts of the body. Again, the occupational therapist has a specialized knowledge and skill which can be acquired only outside the field of medicine, and the almoner is primarily a social worker, bringing into the Health Service knowledge and experience gained in the social science departments of universities and in fields of social survey other than health.

Indeed, a minority report by the almoners and the occupational therapists disputes the term "medical auxiliary," which in their contention denotes an untrained or partially trained person—e.g., a nursing auxiliary. They prefer the term "non-medical professional and technical staff," like the "non-professorial teaching staff" in universities. It is an indication of the difficulty of this inquiry that there are three minority reports which are signed by all the medical auxiliary representatives of four of the eight committees, though their reservations are only to portions of what is recommended. And one minority report falls foul of the report of another minority.

1 *Reports of the Committees on Medical Auxiliaries.* Cmd. 8188. H.M.S.O. 5s. net.

### The Present Position

At the end of 1949 the number of persons in England and Wales and in Scotland working in the National Health Services as auxiliaries was as follows:

| | | | |
|---|---|---|---|
| Almoners | 975 | Occupational therapists | 980 |
| Chiropodists | 388 | Physiotherapists | 4,019 |
| Dietitians | 177 | Radiographers | 2,444 |
| Laboratory technicians (including students) | 3,195 | Remedial gymnasts | 146 |
| | | Speech therapists | 121 |

About 84% of these were employed whole-time. Only among chiropodists and speech therapists was there a majority of part-time workers.

It will be remembered that as a result of the efforts of the British Medical Association and the Society of Apothecaries of London a Board of Registration of Medical Auxiliaries was formed in 1936. This board is on a voluntary basis and as such is subject to certain handicaps. Of the qualifying bodies now under consideration, two only—the Society of Chiropodists and the College of Speech Therapists—insist upon their members registering with the board. In some of the categories only a small proportion have applied for registration.

What is now proposed by the eight committees is the setting up of a council for Medical Auxiliary Services in the National Health Service to maintain statutory registers of persons qualified for these employments, to recognize schools, courses, and examinations, to keep under review the relation of supply to demand over the whole range of the services, and, among other functions, to ensure that the training in the medical auxiliary services keeps pace with the advances in medical thought and practice. While the diversity of the services is recognized, it is felt nevertheless that a single council is preferable to independent group councils as being more likely to command respect among the auxiliaries themselves, as well as in the medical profession and among the general public. Registration by the council would be an essential qualification for work in the National Health Service.

### Central Council and Professional Committees

In setting up this central council the pattern of the General Medical Council and similar bodies would be followed. It is proposed that it should consist of four members appointed by the Privy Council, under whose aegis it would function, three by the Minister of Health and the Secretary of State for Scotland, seven by the Royal Colleges and Corporations, and one by the General Medical Council. There would be six representatives of the medical auxiliaries themselves. It may be asked why the figure is limited to six when the inquiry has necessitated eight committees to cover the different categories. It is suggested that the function of these medical auxiliary representatives on the council would not be to put forward the views of a particular category, but to supply the point of view of the medical auxiliary services as a whole. Thus it will not be necessary to have every one of the medical auxiliary services represented, unless matters pertaining to it alone are brought forward, when special representation may be arranged.

In addition to the council there will be a series of professional committees, the majority of whose members will be experts in a particular field of auxiliary service. The chairmen of these committees will be appointed by the council, but the vice-chairmen will be appointed by the committees themselves, and these vice-chairmen will form a kind of electoral college for the appointment of the six representatives of the auxiliaries on the council. The number of these professional committees is not laid down. As a rule, each

of them would be concerned with a single service, but group committees can be set up for co-ordination between related services. The council would depend upon these professional committees for information, advice, and assistance.

The question of the relation of the proposed council to the professional associations, such as the Chartered Society of Physiotherapists, the British Dietetic Association, or the Institute of Almoners, has to be considered. Some of the work of these associations must be taken over, but it is thought that it would be unsound for the central council to undertake training courses or examinations, and, of course, the council would have nothing to do with auxiliaries working outside the National Health Service. The expenses of the council and its committees should be met out of N.H.S. funds, as should the fees of applicants already employed in the Service when the registers are opened. It is considered that, except medical laboratory technicians, student medical auxiliaries should themselves meet the cost of their training. The local education authorities would be the most appropriate source of financial assistance if this is needed.

### Minority Objections

As already stated, there are three minority reports, all of them in the names of representatives of the auxiliaries. The almoners and occupational therapists and speech therapists, while in favour of statutory registration, hold that the proposals involve the possibility of more than one standard of basic qualifications being recognized within a single profession. They consider that the establishment of a central controlling council to direct a number of distinct professions can have only a stultifying effect on the work of the professions concerned. The assumption that doctors, by virtue of their medical training and experience, can satisfactorily control the curricula of training and methods of work of the professions under review is, in the view of these reservationists, not in accordance with the facts.

The physiotherapists and remedial gymnasts object also to one council for all medical auxiliaries. What they want is a separate council for the three professions—physiotherapists, remedial gymnasts, and occupational therapists. On the other hand the occupational therapists dissociate themselves from the suggestion that they should be included for registration purposes in a rehabilitation group with physiotherapists and remedial gymnasts. They urge that this would give an unbalanced emphasis to the work of the occupational therapist in the purely physical field and would diminish the psychological aspect of occupational therapy. They also feel that there has been too much concentration on registration, which is only one of a number of equally important considerations in supplying an efficient occupational therapy service.

### Almoners: Dietitians: Speech Therapists: Chiropodists

The remainder of the report is occupied with the separate services. Between 3,000 and 3,500 almoners are probably needed in the hospital service, and, if no more is done than replacement of normal wastage and opening of new departments where the need is particularly pressing, 150 new almoners will be wanted each year. It is considered that almoners might well be relieved of some clerical duties, and employing authorities are invited to review the work done in their almoner's department so that the best use may be made of the almoner's time. The training now provided by the Institute of Almoners is regarded as suitable.

Trained dietitians should be available throughout the hospital service. Ideally there should be a dietitian for every 150 beds in hospital. The great majority of hospitals have no qualified dietitian on the staff. If only one were appointed by each management committee and board of governors about 400 would be needed; actually there are fewer than 200. There are only four places in Great Britain —two of them in Scotland—in which a diploma course in dietetics can be taken, and it is felt that arrangements should be made to provide a school to serve students in the Midlands and the south of England. The standards which students are required to reach for membership of the British Dietetic Association are satisfactory.

The majority of speech therapists are employed in the school medical service, and the committee feels that in this respect there should be closer integration with the hospital service. There is need for a total of at least 750 speech therapists. The number qualifying each year is about 60. The demand in the N.H.S. is restricted by financial considerations and questions of accommodation, and probably during the next few years the present increase will suffice to meet the demand (as distinct from the need). The course of training in the College of Speech Therapists is adequate, but medical representation on the examinations board is small. It should be adequate to cover the fields of oto-laryngology, neurology, and psychiatry.

A chiropodist should be available in every general hospital. There appears to be a considerable demand for chiropody at clinics established by local authorities. The examinations sponsored by the Society of Chiropodists for students from schools it recognizes provide an adequate test of proficiency, but it is suggested that the examinations should be open only to those who have attended a full-time course of study. The committee is not satisfied that the qualifications offered by other organizations provide an adequate criterion of competence for employment in the N.H.S. One recommendation is that local authorities should be enabled to provide chiropody, possibly under Section 28 of the Act.

### Radiographers: Medical Laboratory Technicians

There seem to be no means of assessing accurately how many radiographers will be needed in the National Health Service, but it is regarded as unsafe to assume that the rate will continue to increase at the pace of the past 20 years. The average working life of the radiographer is put at 10 years. The shortness of this period is due to the fact that the majority of radiographers are women, among whom there is much wastage through marriage. Taking this basis, the present output of students should suffice to meet the present demand. The board of examiners of the Society of Radiographers, which numbers over 60, is regarded as unwieldy. The committee concerned thinks it would be an advantage if the full executive responsibility for the conduct of examinations were given to a small examining board representative of the medical profession, hospital physicists, and radiographers. Membership of the society indicates a satisfactory standard. Although members should be encouraged to take the fellowship, this should not be made a requirement for any particular appointment.

The need for medical laboratory technicians in the National Health Service is permanent, but the extent of the need will be directly related to developments in pathology It is considered unlikely that there will be any large alteration of the position during the next five years. The examinations of the Institute of Medical Laboratory Technology are judged satisfactory, but the committee adds that it is important that the theoretical side should never be allowed to overshadow the practical nature of the examination.

### Physiotherapists: Occupational Therapists

The evidence of the many witnesses before the committee on physiotherapists was that the work of the physiotherapist merges with that of the remedial gymnast and the occupational therapist. No hard and fast line can be drawn. One witness stated that a general hospital with most special branches of medicine and surgery and with an efficient rehabilitation department requires six physiotherapists to every 100 beds. The committee believes that, with an adequate service of consultants available in the hospitals, the number of physiotherapists required would be about 5,500. The present output from the recognized schools is over 500 a year, and it should be possible to maintain the present numbers and gradually build up to the full demand. The training given at the schools recognized by the Chartered

Society is comprehensive. More use should be made of teachers of physical education with remedial qualifications as part of hospital rehabilitation teams, particularly in rural areas. More economical employment of the existing supply of physiotherapists in the N.H.S. could be achieved by the establishment, wherever possible, of physical rehabilitation departments, which would include physiotherapy, occupational therapy, and remedial gymnastics. To prevent unnecessary work in the physiotherapy department, treatment should be prescribed in all cases by a medical or surgical consultant, and in every hospital one consultant, preferably a specialist in physical medicine, should be given the oversight of the department.

The need and the demand for occupational therapists in the N.H.S. are difficult to estimate. In view of financial restrictions and other difficulties it is not considered that the figure will rise much above 1,000, at which it stands at present. In general hospitals at least one occupational therapist should be employed for every 100 beds. The training which is given at seven schools in England and one in Scotland is considered adequate. In England all the schools follow a syllabus based on the examination requirements of the Association of Occupational Therapists. It is suggested that more use should be made of medical practitioners in training occupational therapists.

The 25 appendices to the report furnish an instructive guide to the syllabus and scope of training, examination regulations, and character and volume of work in these various fields of medical auxiliary employment.

## AT THE OPHTHALMOLOGICAL CONGRESS

The work of Allbutt, Jonathan Hutchinson, Gowers, and a multitude of other clinicians has forged a permanent link between ophthalmology and general medicine. It was encouraging, therefore, to see this traditional relationship being maintained at the annual congress of the Ophthalmological Society of the United Kingdom, which was held in London from March 29 to 31.

### Therapy in Diseases of Doubtful Aetiology

Professor E. J. WAYNE took the opportunity to give a warning against the indiscriminate use of A.C.T.H. and cortisone: both these powerful substances could produce harmful side-effects, not only while they were being administered, but also as a sequel to prolonged use or after their sudden withdrawal. Professor G. W. PICKERING reminded the congress that the pharmacological action of these hormones was exceedingly complex, and that much about their action still remained to be elucidated.

Dr. F. DUDLEY HART said that the search for a specific organism in the tissues of people suffering from rheumatic disorders might well have obscured the aetiological issues. More than half a century had elapsed since Still[1] had pointed out the association between ocular lesions and chronic juvenile polyarthritis. At that time syphilis, tuberculosis, and a number of other diseases were known to be capable of attacking the eyes as well as the joints. More recently Reiter's disease had been described, and Behcet's syndrome and other conditions had been added to the list of maladies for which general practitioners and eye specialists were equally concerned to find a remedy. There was no place in these conditions for blunderbuss therapy—the prescription of sulphonamides together with penicillin or one of the newer antibiotics in the hope of achieving cure by summation of effect; in practice the reverse might occur, as sometimes these agents were mutually antagonistic.

### The Eye in Pharmacology

Sir HENRY DALE, who delivered the Bowman lecture, emphasized the merits of the eye as a testing-ground for the pharmacological action of alkaloids and other substances. Movements of the pupil, nictitating membrane, and orbital muscles of experimental animals could be watched in detail, and the changes brought about by drugs could be recorded precisely. The accessibility of the eye to observation was particularly important in detecting evanescent effects, such as those produced by acetylcholine. Pharmacological information thus obtained was applicable to systemic as well as to ocular therapy, so that this use of the eye should be regarded as a further bond between ophthalmology and general medicine.

### Retrobulbar Neuritis in Measles

Retrobulbar neuritis is a rare complication of measles. Mr. M. H. WHITING, the president of the Ophthalmological Society, described the case of a 6-year-old girl the vision of whose right eye became blurred on the fourth day of an attack of measles. On the fifth day the right pupil gave no response to direct light, and she was unable to distinguish between light and darkness with the affected eye. Ophthalmoscopy showed no abnormal signs in the fundus. Two days after the onset of ocular symptoms vision began to improve, and recovery was apparently complete two days later. Retrobulbar neuritis might occur as a complication of certain other febrile illnesses, including influenza, but most cases were due to disseminated sclerosis. In these there might be an interval of many years before further signs of disseminated sclerosis became manifest, and as a result many cases of retrobulbar neuritis had been wrongly attributed in the past to disease of the sphenoidal sinus.

### Dangers of Irradiating Rodent Ulcers

In his presidential address Mr. Whiting discussed rodent ulcers. He pointed out that well over half of the total number of rodent ulcers attacked the soft parts in the immediate neighbourhood of an eye. Early diagnosis was particularly important, because radical removal was nearly always possible so long as the growth did not exceed one inch in diameter and had not yet invaded the underlying bone. As neither of these things was likely to happen for years it might seem strange that advanced cases were ever seen in practice, but the growths were painless when still superficial and advanced so slowly that many patients did not think of seeking advice until extirpation had become impossible. Owing to the flexibility and rich blood supply of the skin covering the eyelids and adjacent areas of the face, gaps that remained after excision of small growths could usually be readily closed; larger gaps might require flaps from bordering skin or even a pedicle slung from the forehead. Advanced cases might demand Thiersch grafting, but elaborate plastic procedures should if possible be avoided because they sometimes masked recurrences.

"But is it not the custom nowadays," some will ask, "to treat all these ulcers by irradiation?" Mr. Whiting's experience would compel him to answer that such a custom, if it is a custom, is not good. He admitted that irradiation gave good results in certain growths shown histologically to be of the infiltrative type, but more recent knowledge would, he thought, make surgical removal as effective, if not more so, in these cases. Sir John Parsons used to teach, more than 20 years ago, that cure following irradiation of a rodent ulcer might be spurious, because the proliferation of malignant cells might continue below the surface, like a fire in the hold of a ship, until bone itself was invaded and surgery was no longer feasible. Mr. Whiting stated that in some cases damage had been done to an eye, in spite of the customary screening precautions having been observed during irradiation. Such damage tended to be concentrated upon the retinal blood vessels: thus haemorrhages and exudates upon the retina, followed by shrinkage in the calibre of the arteries, could be observed by ophthalmoscopy; cataract and secondary glaucoma had also been reported as sequels of irradiation in the neighbourhood of the eye. Epiphora was a less serious complication than damage to sight, but it could nevertheless be troublesome,

1 Still, G. (1897). *Med.-chir. Trans.*, **80**, 47.

and he drew attention to the ease with which rays directed near the lower canaliculus and lower pole of the lacrimal sac could provoke fibrosis in those structures, with resulting blockage of tears. In short a large majority of these neoplasms could be cured by excision at the first attempt, and histological examination would show whether operation had in fact been sufficiently extensive. The cosmetic results of irradiation compared favourably with those of surgery, but irradiation, in spite of screening devices, threatened the integrity of the eye and might also damage the lacrimal apparatus.

## A.C.T.H. AND CORTISONE IN DISEASE

An April 5, under the auspices of the Society for Endocrinology, Dr. J. S. L. BROWNE, Professor of Medicine at the McGill University Clinic, Royal Victoria Hospital, Montreal, delivered a notable lecture on "A.C.T.H. and Cortisone in Disease" at the Royal Society of Medicine. He first expounded the relationship of the general adaptation syndrome, as elaborated by Selye, to the action of these substances. He showed how the excretion of urinary corticoids was increased by a stress such as a long route-march; how it rose in pneumonia and after operations, only to fall with recovery. In pregnancy, too, the urinary corticoids rose, there being two peaks, one at about the sixtieth day and the second at about the seventh month; the values reached were similar to those seen in Cushing's syndrome, and Dr. Browne thought that pregnancy could be regarded as a physiological Cushing's syndrome. He cited another case where a sudden emotional stress caused a dramatic rise in the corticoid excretion.

### Effects on Nitrogen Balance

Acute trauma of all sorts, it was well known, caused nitrogen loss—the loss coinciding with the increased adrenocortical activity. But long-continued stress was accompanied by a fall in corticoid excretion, and a negative nitrogen balance was changed into a positive one. These findings had led Drs. Albright and Browne to elaborate the hypothesis that a rise in corticoid production was accompanied by increased protein destruction. Discrepancies, however, soon appeared, and it had become necessary to modify this view. Dr. Browne now believed that in general the cortical steroids made the body protein more readily mobilized, and what happened to the protein then depended upon the state of the body—in acute trauma, the protein was deaminated and lost; in pregnancy, it passed into the highly anabolic area of the uterus and foetus and was retained. He believed also that there was a hierarchy of tissue requirements for protein—which might change in different circumstances. The effects depended on the state of the organism as a whole, and to illustrate this point he quoted the metaphor, suggested by Selye, of opening the window of a room—if it was hotter outside, the room got warmer, but if it was colder outside, the room got colder. The variability of the effects of cortisone, which could be explained on this view, were well shown by the failure of wound healing while under A.C.T.H. treatment in one case, but its normal occurrence in similar circumstances in another.

Dr. Browne then skilfully developed the thesis that A.C.T.H. and cortisone did not merely mobilize protein; they also caused shifts in electrolytes (sodium retention, potassium loss), water, vitamin C, histamine, the erythrocyte maturing factor, and so on. He described the effects of these hormones in a wide variety of diseases, showing how they could improve nephrosis, scurvy, pernicious anaemia—though he emphasized that he was not suggesting A.C.T.H. as treatment for these last two diseases—chronic pulmonary fibroses, asthma, etc. Remissions, however, were of variable duration and relapses usually occurred sooner or later. He pointed out the untoward psychological reactions which might be encountered, and said he thought that A.C.T.H. merely brought out what was already there. By having the patient draw a male and a female figure at varying stages in treatment, fascinating changes were produced, coinciding with the patient's mental state—to the great amusement of the audience.

### Cortisone and Tuberculosis

The use of cortisone in pulmonary tuberculosis demanded the greatest caution; while under treatment, the patient usually seemed much improved, but the walling off of the lesion might be undermined so that on stopping treatment dangerous, or even fatal, exacerbation might follow. However, Dr. Browne described two cases of Addison's disease who had pulmonary tuberculosis and whom, because of the grave outlook, it was felt justified to treat with cortisone, streptomycin, and P.A.S. One, who had developed crippling contractures of the legs under previous D.C.A. treatment—a very rare complication—gained 50 lb. (22.7 kg.) in weight, and showed all-round improvement. Her tuberculosis cleared, as did the pigmentation. In the other case general improvement also occurred in the Addisonian symptoms, but the pulmonary lesion did not change. But unless there were some serious complication, such as in the two cases above, he thought it hazardous to use A.C.T.H. or cortisone in tuberculous patients.

Finally, Dr. Browne drew attention to the fact that these hormones masked the symptoms of disease and obscured the criteria by which we were accustomed to estimate the severity of illness. He did not think they could cure many diseases, but they altered the body's reaction to them. They might exert a protective effect in some acute conditions—as in rheumatic fever, for example. He drew the picture of disease in general as an iceberg, with one-eighth above water—the observed specific reactions of the body to disease—and seven-eighths below water—the general reaction of the body. A.C.T.H. melted away some of the underwater portion, and caused the peaks to disappear below the surface—temporarily, and sometimes intermittently. There was, in fact, a vast common underground of many different diseases; this it was that A.C.T.H. and cortisone affected, and this explained their apparent beneficial effects in such widely different disease conditions. He also emphasized the possible importance of emotional stresses in influencing disease, since it had been shown that such stresses could liberate adrenal cortical hormones within the body.

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The chief item of medical interest at the Physical Society's annual exhibition—held as usual in the somewhat gloomy and forbidding laboratories of the Imperial College in South Kensington, this year from April 6 to 11—was undoubtedly the Colour Group's display on the evolution of the study of colour vision. Beginning with Robert Boyle's *Experiments and Considerations upon Colours, with Observations on a Diamond that shines in the Dark* (1664), from which the first practical demonstration was drawn, the show moved swiftly on through experiments by Newton and Goethe which the visitor could see for himself, to the Purkinje phenomenon, and to the discovery by Chevreul in 1835 of simultaneous contrast: that adjacent colours influence one another's shade, a very apt discovery for the director of the Gobelin tapestry factory to make. Maxwell's coloured spinning wheel was there, and Grassman's laws of colour, and the Lovibond tintometer, the first attempt (1885) to measure colour accurately, introduced to determine the quality of beer. An interesting demonstration by Willmer showed every normal visitor to the exhibition that he had an area of blue-green colour blindness in the central foveal region of his retinae. This was followed by the Ishihara colour plates, and the display wound up with explanations of Granit's work on the electroretinogram, recording electrically the nervous impulses from single cells of the retina when they are stimulated by monochromatic light of different wavelengths. Most of the rest of the exhibition was given over to electronics in one form or another, and cathode-ray tubes were everywhere. There were, however, interesting demonstrations of ultrasonics, and of radiation monitors, and displays by Government laboratories of studies on the adequate lighting of schoolrooms, and similar topics.

# Reports of Societies

## HEADACHE

A meeting of the Section of General Practice was held at the Royal Society of Medicine on March 21 to discuss headache. The president, Dr. G. F. ABERCROMBIE, was in the chair. The opener, as is the custom in this Section, was a general practitioner, Dr. G. J. V. CROSBY. In an entertaining and constructive paper, Dr. Crosby drew on his experience in practice over the last 25 years. He began by citing the histories of four of his own recent cases of headache, illustrative of the wide variations which occur in character, situation, and severity. The first case was that of a man, with a recent history of headaches, to whom he was called urgently on account of very severe frontal and occipital pain of sudden onset and accompanied by vomiting. Examination showed marked neck rigidity. A diagnosis of subarachnoid haemorrhage was made, subsequent necropsy confirming this. Dr. Crosby emphasized the comparative rarity of this condition in general practice.

### Hexamethonium Treats the Symptom

The other cases included classical migraine and frontal headache with no physical signs except loss of translucency of the antra and hypertension. Dr. Crosby commented that he had found hexamethonium bromide effective in relieving the headaches of hypertension even in cases where it had little effect on the blood pressure. In arriving at the diagnosis in a case of headache, a detailed history was invaluable, and the following information should be sought for specifically. Where is the headache; what is its character; is it continuous or intermittent, worse in the morning or the evening, preceded by a warning or influenced by posture? How long does it last; does it prevent sleep? Inquiry should be made about family history, employment, or previous head injury. As well as a general medical examination Dr. Crosby stressed the importance of testing the urine, examining the fundi, and taking the blood pressure in every case of headache.

In infectious diseases the headache was usually in direct proportion to the amount of fever present, but occasionally it was a presenting symptom, as in typhoid fever, or in polio-encephalitis, which was frequently heralded by a blinding pain referred to the occiput. In obscure cases the possibility of uraemia should be remembered. An important point, insufficiently appreciated, was that Ménière's disease might be accompanied by headache, usually unilateral, often continuous, and referred to the same side as the diseased labyrinth.

### "Agony" Gives the Diagnosis

Dr. Crosby's comment on the neurotic headache, especially if there was a compensation factor, was, "Work appears eminently undesirable . . . the use of the word agony may help to make the diagnosis." The importance of finding positive evidence of psychological disorder before making a diagnosis of neurotic headache was stressed.

One of the most difficult recurrent headaches to treat was migraine. Ergotamine tartrate, in doses of up to 0.5 mg. dissolved under the tongue, was effective in some cases, but occasionally produced nausea and vomiting. Twenty drops of solution of dihydro-ergotamine given by mouth hourly until the attack was over was equally effective, and was free from unpleasant side-effects. The occurrence of migraine at the time of menstruation in women might be due to a disturbance of water balance in the days preceding the period, and might on occasion be relieved by a course of progesterone 2 mg. or more given on alternate days.

Finally Dr. Crosby reminded the Section that "headache in an adult may mean much, or nothing much; in a child, watch your step."

Dr. DESMOND CURRAN had analysed 300 cases of psychiatric disorder. While agreeing that there was much overlap in the symptomatology he found that depression, anxiety, and hysteria were the commonest psychiatric diagnoses. Of the 300 patients 118 had head complaints of one sort or another, and in the diagnostic groups mentioned no one group showed a specific frequency of these complaints, although constant headache sometimes occurred as the sole symptom in rigid hypochondriacs. It was interesting that the complaint of headache as such was relatively uncommon in psychiatric practice, perhaps because most cases were treated by their practitioners or seen by neurologists, and perhaps because many psychiatric patients had a conscious or unconscious desire to have a physical disease and therefore start with a physical complaint. By the time they reached the psychiatrist they were more prepared to discuss their real symptoms, their depression, or their inability to concentrate. It was notable so far as their head symptoms were concerned that most of them had an unpleasant feeling or emotion, rather than a sensory experience. A proprietary attitude to their symptoms was common and the capacity to perform unpleasant tasks most affected. In conclusion Dr. Curran emphasized that the head pains he came across were not headaches.

### Head Pains and Headaches

Dr. DENIS WILLIAMS reminded the Section of Spriggs's Croonian Lecture in 1935, in which he described a series of 500 cases of which only 2% had organic intracranial disease. The symptom of headache was so common that if the patient had never had one he was subjected to investigation. Dr. Williams then discussed the anatomy of headache, pointing out that it is the extracranial structures which are pain-sensitive, the intracranial structures being quite insensitive, including the thalamus, the ependyma, the dura except the part adherent to the base of the skull, and all the veins, except where they enter the large sinuses. The pain-sensitive structures consisted of the large vessels, arteries at the base of the brain, and certain arteries before they entered the brain substance, and in addition nerves which traversed the dura. The trigeminal nerve supplied all supratentorial structures; the glossopharyngeal, vagus, and upper three cervical nerves, the infratentorial. Pain was referred to the distribution of these nerves, and thus any structure situated in the anterior fossa gave rise to pain anterior to a coronal intermastoid plane.

Physiologically there were three ways in which pain might arise from pain-sensitive structures, by distortion, displacement, or distension. Very many headaches arose because of a disturbance of the normal relationship between the pressure inside an artery and that outside. A simple example of this was the low-pressure headache which not infrequently followed lumbar puncture. If the intracranial pressure was raised by tipping the legs up, the headache would go. But if the pressure was raised by compression of the jugular veins then the headache would be aggravated, because it was due to low pressure outside the veins and compressing the jugulars merely increased the discrepancy.

### Procaine in Treatment

There was no doubt that the head pains of psychiatric disorder had a physical basis and arose from the same anatomical and physiological mechanisms as those of organic disease. The headaches of an anxiety state might be due to associated activity of frontal and occipital muscles; certainly if the motor nerves were blocked the headache would disappear.

In the subsequent discussion several speakers mentioned the frequency of local rheumatic conditions as a cause of headaches in general practice. In several cases there were tender spots in the frontal, occipital, and temporal muscles, injection of which with procaine led to relief of the pain. One speaker confirmed the relationship of increase in body weight in the premenstrual period to the occurrence of attacks of migraine, the frequency of which was considerably diminished by progesterone therapy.

# Correspondence

## Conception and Oligozoospermia

SIR,—The Biological and Medical Committee in its Report to the Royal Commission on Population (*Papers of the Royal Commission on Population*, volume 4. *Report of the Biological and Medical Committee* (1950). H.M. Stationery Office) observed that between 5 and 8% of married couples are involuntarily childless (p. 43) and that about one-third of the husbands in infecund matings have been found to show gross deficiency in spermatogenesis (p. 40). Thus about two or three out of every 100 husbands will be found, usually much to their surprise and mortification, to be profoundly lacking in sperms. Many of these husbands have no reason to suspect that they are suffering from this condition until, during the course of routine fertility investigations conducted when they have begun to wonder why their family is so long in appearing, a semen test reveals the defective spermatogenesis. They then feel themselves to be guilty of failing in their duty to their wife, and in their remorse are anxious to leave no stone unturned to rectify the fault. The responsibility of their medical adviser is therefore considerable. Is he to tell them that except on very rare occasions, such for instance as the stimulation of spermatogenesis by specially prepared pituitary gonadotrophic extracts (not yet on the market) in cases of hypogonadotrophic hypogonadal aspermia, there is no effective treatment for their condition, though there have been examples of men with persistently low sperm counts eventually achieving parenthood spontaneously? Or is he to advise them to undergo treatment, and, if so, what treatment?

Presumably the purpose of the memorandum by Miss Moore White and Dr. Mary Barton (*British Medical Journal*, April 7, p. 744) is to advocate treatment, for they say, "There seems little doubt that treatment in all three cases accelerated the achievement of pregnancy." But what treatment? They refer to (1) changing the husband's job so that he does not work so hard, (2) restriction of smoking to ten cigarettes a day, (3) sulphonamides, (4) iron, (5) arsenic, (6) "B vitamins," (7) liver preparations, (8) serum gonadotrophin, (9) general dietary measures, (10) planned intercourse, (11) supplementing the protein in the diet, (12) vitamins A and D, and (13) testosterone implants.

Before accepting the very important assumption they have made, one must surely scrutinize their case protocols very carefully. Unfortunately the information given in these is insufficient to enable one to appraise them accurately. For instance, in the reports of the semen tests reference is sometimes made to "occasional spermatozoa," whereas in other instances actual counts, such as 0.025 millions per ml. are given. Is there any significant difference between these two descriptions? In Case 1 it is recorded that in a post-coital test sperms were not found in the cervix. Was the test performed during the ovulatory phase? The husbands in Cases 1 and 2 looked "pallid" and "pale" and were given full courses of iron and arsenic, a liver preparation, and B vitamins or vitamins A and D, but nothing is said about haemoglobin estimations or blood-counts. In Case 2 the husband's "diet was deficient in protein." To what extent? And he "was told how to supplement his diet." How? Surely we are entitled to this information, especially in Case 2, where the only treatment consisted in dietary measures and correction of an anaemia which was apparently presumed but not demonstrated. Then there are the semen tests. Four were performed in Case 1, the last nine months before the wife became pregnant, no test being made to ascertain the husband's spermatogenic status at the time or shortly after his wife's conception. In Case 2 only one semen test was performed, and it is possible that further tests might have revealed a less severe degree of spermatogenesis. No test was performed after the wife became pregnant. In Case 3 intercourse was "infrequent." Does that mean on an average once a week, once a month, or once a year? And after a testosterone implant the libido improved. Did the frequency of intercourse increase?

In the absence, then, of more detailed information I submit that each of these three husbands belonged to that group in which, in spite of grossly defective spermatogenesis, conception may occur on very infrequent occasions. In addition it should be pointed out that the wife in Case 1 had a severely ulcerated and infected cervix which responded well to treatment: this may then have been as serious an infertility factor as the defective spermatogenesis. Finally, in Case 3 the increase in frequency of intercourse, if indeed this occurred, may have contributed to the wife becoming pregnant.

I do not feel that Miss Moore White and Dr. Barton have justified their claim that treatment of the husbands accelerated the achievement of pregnancy. Furthermore, I feel that in the absence of more convincing evidence than has been brought forward to date one's duty to the infertile couple is to tell them that there is no effective treatment yet available for defective spermatogenesis.—I am, etc.,

Fertility Clinic,
Chelsea Hospital for Women. P. M. F. BISHOP.

## Breast-feeding

SIR,—I am stimulated by Dr. Charlotte Naish's excellent article (March 24, p. 607) to raise a question which has been troubling me for some time. Not infrequently one is consulted by young mothers, recently confined, whose opening gambit is, "I want some tablets to take away my milk." On asking the reason for this request one is told that the mother (or even the father) does not approve of breast-feeding, for a variety of reasons. Some I have heard recently are, "It isn't nice"; "It makes a mess of my clothes"; "It spoils my figure"; "I can't go to the pictures without the milk wetting my clothes."

I confess that I am angered and annoyed by these selfish and foolish women, but try to reason with them and explain the benefits of breast-feeding to both mother and infant. Usually this avails nothing; and my problem is whether to refuse point-blank to aid and abet these patients to evade their natural function, or to say little and hand over the prescription for stilboestrol, soothing my conscience with the thought that the infant is doomed to the bottle whatever I do. This is an ethical question, and I have not seen it discussed anywhere. It would be interesting to learn the views of others and to know if a definite ethical ruling can be given.

I should perhaps point out that I have no hesitation in assisting the suppression of lactation in those unmarried mothers who have to go out to work all day; or in those cases where a midwife requests stilboestrol for her patient (sometimes, I regret to say, on pretexts that Dr. Naish would regard as flimsy if not inadequate.—I am, etc.,

Wakefield. J. D. BOTTOMLEY.

SIR,—Dr. Charlotte Naish's address (March 24, p. 607) to the Section of Child Health is provocative. She makes, I think, two main points. The first is that breast-feeding is better than bottle-feeding, and the second that the care of the nursing couple is best placed in the hands of the family doctor.

The first point is one to which lip service is paid. All the evidence which Dr. Naish can produce will be of great use in trying to convince mothers and those who care for them that what to many of us seems a self-evident truth can be proved. I am sure that the extension of breast-feeding depends on doctors and nurses being convinced that it is the better way.

The second point is more debatable. The best person to care for the nursing couple is the person who can give informed regular care and who is interested. I think Dr. Naish cannot hope to convert the majority of family doctors to care for the nursing couple along the lines on which she conducts her own practice. Each practitioner has his or

her own enthusiasms, many do not do obstetrics, and many are not interested in the work of preparing for and maintaining breast-feeding. If Dr. Naish could infect the health-visitor organization with her enthusiasm and further the teaching to midwives and health visitors of the techniques which she and Dr. Waller use so effectively, we could expect an extension of breast-feeding. The health visitor is highly trained, hard working, tolerant, and usually a well-balanced person. She already provides the bulk of the continuing care which Professor Moncrieff and Dr. Naish underline as being a necessity in infant care. She could work with the family doctor as well as with local-authority doctors. Already she is the professional friend and welcome visitor in the families of the nursing couple. She knows them and their milieu well, and in many cases by virtue of her relation to the other social services knows more of the family situation than a family doctor or parish priest. I am speaking of the London area in particular.

Finally, may I add a suggestion that to ease the tensions of the puerperium we should abolish the practice of weighing the baby at birth, with all the varying practices about subtracting hypothetical cord weights and so on, and let us weigh the baby about the seventh or tenth day?—I am, etc.,

London, N.2. JEAN LAWRIE.

SIR,—As an infant-welfare-centre medical officer and also as the mother of two small children, I greatly appreciated Dr. Charlotte Naish's article (March 24, p. 607) and would like to offer a few personal observations.

I usually meet mothers for the first time during the "third week drop" phase, and I fully agree with Dr. Naish's views that ultimate success in breast-feeding depends, to a greater extent than at present realized, on antenatal education of mothers and also on the views of the doctor and/or nurse supervising the confinement. Complete avoidance of the use of feeding-bottles by giving all complements and other fluids from a spoon can be undertaken from birth and is the surest way to encourage perseverance with breast-feeding. I find it greatly encourages mothers to point out to them that spoon-feeding from the beginning means less trouble later with the introducing of mixed feeding, since the infant has then only to learn to accept other flavours and consistences and not an entirely fresh method of ingesting food.

There are two fallacies I frequently encounter and to which I would like to draw attention. I think it is an accepted fact that the supply of breast milk is maintained by the stimulus of suckling—why then is it still believed that missing out a feed will increase the supply available for the next feed? I constantly discover that mothers with poor milk supply have been advised to give an artificial feed in place of a breast feed instead of as a complement after the breast feed, thus ensuring that the child will very shortly be entirely artificially fed. I also believe it to be a mistake to advise any mother, unless she is most unusually blessed with an overwhelming abundance of milk, to give one breast only at each feed, as this very soon reduces the supply.

In conclusion, I would like to say that I agree enthusiastically with Dr. Naish's suggestions for obtaining an ideal relationship between doctor, mother, and baby. Mothers seem to need much patient understanding and advice on problems not usually regarded as within the proper province of doctor or nurse. Believing as I do in prophylaxis wherever possible rather than treatment of disease, I would far rather advise on laundering problems than prescribe for sore buttocks.—I am, etc.,

London, S.W.7. KATHERINE ELLIOTT.

## Bedtime Problem Solved

SIR,—Professor R. S. Illingworth's article (April 7, p. 722) reminds me of a stratagem often useful when the infant, having been put to bed, refuses to be left. Soothe it in the usual way and then retire, making appropriate "bye-bye" noises; but at the first hint of a whimper return *at once* and repeat the soothing; if the incipient emotion has been caught quickly it will die down again in a few seconds. After a few repetitions of this manœuvre the obtuse infant, dazzled by its own omnipotence, does not notice that the response has declined to a mere token, such as popping one's head round the door. Soon even that edifying spectacle palls, and the devoted parent is permitted to creep away. The great thing is to respond immediately, thereby providing both cumulative reassurance and cumulative depreciation of one's entertainment value.—I am, etc.,

Cambridge. W. E. HICK.

## Syncopal Attack from Bradycardia in an Infant

SIR,—I was most interested in Dr. John K. Wagstaff's article (March 24, p. 614), particularly as recently in general practice I was called to an infant in a syncopal attack which was clinically similar to the recurrent attacks described by Dr. Wagstaff. In this case the precipitating factor appeared to be bronchopneumonia.

The infant, a boy aged 4 weeks, was stated by his mother to have been well since birth, but during the past two days he had refused his feeds. He had developed a cough the previous day. About two hours before I was summoned he had apparently collapsed. When I arrived he was lying still, his face was pale and slightly cyanosed, eyes staring and glazed. Respirations were very infrequent and came in shallow gasps. The pulse was imperceptible. On auscultation the apex rate was found to be 50 and a rough systolic murmur was audible over the praecordium (this later disappeared when the heart rate was increased).

He was given 1 ml. nikethamide intramuscularly, followed after a short interval by a further 1 ml., as there appeared to be no response to the first dose. After three to four minutes respirations became more rapid, his colour improved, and he started moving his limbs. A short while later he was crying fairly lustily, but the cries were punctuated by coughs. The pulse could now be felt and the rate was approximately 150. On auscultation of the chest coarse rales were heard on both sides, more marked on the right than the left. His temperature was subnormal.

No further attacks occurred during the next half-hour, and he was admitted to hospital, where it was confirmed that the primary condition was bronchopneumonia.—I am, etc.,

Worcester. H. P. PHILLIPS.

## Benzyl-imidazoline in Vascular Disease

SIR,—I would like to report a case which, I think, is interesting because of the remarkable response to treatment of a long-standing disability.

The patient is a man aged 69. His right leg is shortened due to an old injury of the hip (1923) and he wears a thick-soled boot. In 1924 he was in hospital with a thrombosis in the left femoral vein and bilateral pulmonary emboli. In 1938 he had a thrombosis in the right femoral vein. Since this time he complained of oedema of both legs to the groin, pain in the feet at night, and inability to walk. He has a motor-driven invalid carriage from which he had to be helped out to his chair. In September, 1950, he slipped while this was being done and grazed the skin of his left leg, and after two weeks the wound had failed to heal.

On examination there was gross oedema of both legs to the groin and also a purple discoloration around both ankles, especially on the left, partly covered by thick greasy scales. There was a very superficial wound about 1 in. (2.5 cm.) diameter on the front of the left leg just above the ankle, with a slight acute inflammatory reaction around it. Both feet were extremely cold.

He was given 150 mg. of "priscol" (2 benzyl-4:5-imidazoline hydrochloride) daily by mouth divided into three doses, and at the end of one week he had no pain in the feet at night, and the feet were warmer.

At the end of the second week the wound had healed (without any other treatment). The feet were considerably warmer, and there was slight diminution of oedema and discoloration.

At the end of the first month there was only slight oedema and the discoloration was much diminished. The patient was now able to walk across the room unaided, "for the

first time in 15 years," although with difficulty because of the short leg and stiffness. The dose was reduced to 75 mg. daily, and this was given for another month, at the end of which time there was no oedema and only slight discoloration around the ankles. Treatment was then discontinued, and there has been no change in the patient's condition since.

In this case there appears to have been both arterial and venous insufficiency in the legs present for at least 15 years, and considerable improvement after four weeks' treatment.—I am, etc.,

Leeds. A. J. LEVINE.

### Rupture of Bladder in Puerperium

SIR,—Mr. A. L. Deacon's article (March 10, p. 508) about spontaneous intraperitoneal rupture of the bladder in the puerperium prompts me to report the following case.

On January 31 I performed by order of H.M. Coroner a post-mortem examination on the body of a 21-year-old primipara, who had died on the same day, five days after her confinement.

I am indebted to Mr. R. W. Scanlon for the clinical notes of the case. Pregnancy normal apart from constipation. Admitted to hospital on January 24 with vague pains. Labour commenced January 27. Normal delivery of a live male infant (8 lb. 12 oz.). Third stage lasted 20 minutes. Loss about 8 oz. 1 ml. ergometrine given. Second degree tear of perineum repaired with two sutures. On the next day the patient complained of abdominal pains, which were relieved by tab. codein. co. On the day after this she did not complain. In the morning of the 30th, she complained of severe abdominal pain. The abdomen was hard and distended. An enema was given and she passed urine about 1 p.m. In the evening the abdomen was still tense and distended and she vomited twice. Temperature 99° F. (37.2° C.), pulse 100. During the next night she was given an intravenous saline drip and 1/6 gr. (10 mg.) morphine, and a Ryle's tube was passed. The next morning, while she was being prepared for laparotomy, she died.

I performed the post-mortem examination about eight hours after death. The relevant findings were as follows.

The abdomen appeared very distended. Upon opening it, about 1¼ gallons (6.7 litres) of clear, yellow, slightly blood-stained fluid escaped under pressure. All intestines appeared very distended, thin-walled. No evidence of peritonitis. The uterus, hard, well contracted, normal for the fifth day of puerperium. The placental insertion normal. The bladder showed a tear about ¼ in. (0.6 cm.) long in the posterior wall near the fundus, going through the full thickness of the wall. Around the tear was some little haemorrhagic reaction, but the edges did not appear necrotic or gangrenous. On opening the bladder the wall was seen to be a little but not unduly thin, and no papilloma, diverticulum, or other abnormality was seen. It was clear that death was due to paralytic ileus caused by rupture of a normal bladder during, or shortly after, a normal confinement.

I am, of course, aware that one or two cases do not prove anything, but the fact that two cases have apparently been seen during a few months makes one wonder whether the condition is perhaps not quite so rare as generally assumed.

I beg to express my thanks to Mr. W. R. Dauncey for permission to publish the case.

—I am, etc.,

Abertillery, Mon. K. TRIGER.

### Large Ovarian Cysts

SIR,—The interesting communication from Professor R. J. Last (March 24, p. 622) prompts me to record an experience encountered in Sumatra, with special reference to Professor Last's remark: "The extreme degree of abdominal distension and the lack of movable resonance excluded a diagnosis of ascites."

A married Indonesian woman aged 25, who had given birth to her fifth child eight months previously, presented herself for treatment with a gigantic abdominal distension. Her waist measurement was 46 in. (115 cm.) and the distance from the xiphisternum to the symphysis pubis was 26 in. (65 cm.). The abdomen was extremely tense and there was complete lack of movable resonance.

A diagnosis of giant ovarian cyst was made, and treatment was planned along the lines of gradual decompression by periodic paracentesis and eventual laparotomy. However, after evacuation of 32 pints (18 litres) by paracentesis on three separate occasions it became obvious that the fluid was free fluid in the abdomen; the remaining fluid sagged into the flanks and shifting dullness was easily obtained. In addition, a clinically solid tumour estimated at 8 in. (20 cm.) in diameter could now be felt arising out of the pelvis, floating around in the free fluid but apparently attached on the left side of the pelvis.

After further paracentesis and general measures to improve her nutritional state, laparotomy was performed through a subumbilical midline incision. The remainder of the free fluid was sucked out of the peritoneal cavity and a large gelatinous multilocular tumour was found attached to the left ovary. The contents of the tumour were too gelatinous to be aspirated and the incision had to be extended above the umbilicus to allow of its removal. One vascular adhesion to the omentum had to be divided. The peritoneum was studded with gelatinous deposits of pseudomyxoma peritonei, and the appearance of the abdominal cavity was very similar to Professor Last's description of his cases. The tumour measured 10 in. (25 cm.) in diameter and weighed 8 lb. (3.6 kg.). Histology showed it to be a simple multilocular cystadenoma of the ovary. Healing and recovery were uneventful and the patient returned to her native village three weeks after the operation. Follow-up proved impossible.

The total amount of free fluid obtained from the peritoneal cavity was 46 pints (26 litres), i.e., nearly 6 gallons, and it is astonishing to realize that she had been carrying this *plus* an 8-lb. tumour in her abdomen.—I am, etc.,

East Molesey, Surrey. D. E. STEELE, Major, R.A.M.C.

### Hepatitis During P.A.S. Therapy

SIR,—The report by Dr. G. Hurrell (September 23, 1950, p. 729) of a case of acute toxic jaundice encountered during the administration of P.A.S. has had its parallel here.

A Chinese female aged 29 was admitted to hospital on September 16, 1950, with a history of two years' chronic cough, with mucopurulent sputum. During the last six months she had lost weight and had had night sweats. There was nothing of note in her previous or family history.

She was a little wasted, with abnormal physical signs over the apex of the right lung; temperature 100° F. (37.8° C.), pulse 100, both these subsiding to within normal limits after a few days in hospital. Tubercle bacilli were found in the sputum, the E.S.R. (Westergren, 1 hour) was 95 mm., and the *x*-ray film showed fibroid phthisis localized to the right apex. Her weight was 80 lb. (36 kg.).

It was decided to do a localized thoracoplasty after a preliminary period of bed-rest supplemented by P.A.S. On September 23 P.A.S. was begun—15 g. daily by mouth in divided doses. On October 10 her appetite began to fail and during the next ten days she had a mild pyrexia (up to 101.2° F. = 38.4° C.) with malaise. On October 21 the temperature rose suddenly to 102° F. (38.9°C.) and remained thereabouts for the next six days; pulse was 110. The liver was a little enlarged but not tender.

On October 23 an itching rash developed over all four limbs, less on the trunk, consisting of coalescing papules, morbilliform rather than urticarial, and accompanied by fine petechial mottling. The P.A.S. was stopped. On October 28 jaundice was deep; she was dehydrated and very ill. The tongue was parched, and she was very drowsy and disorientated. The skin of the face was dry and was desquamating over the central parts and lips. There was a subconjunctival haemorrhage in the left eye. On November 5 she was comatose, and her relations took her home, where she died a few days later. The urine on November 2 was normal except for the presence of bile and a little albumin; there was no acetone, and there were no casts. A blood film on October 17 was negative for malarial parasites; on October 27 a blood count showed W.B.C. 32,200 with 86% neutrophils. On November 2 the count showed R.B.C. 3,300,200, Hb 60% (Sahli), W.B.C. 31,400, neutrophils 86%. She was unable to take much

food. She was given fluids (including intravenous glucose and saline). Penicillin, 30,000 units three-hourly, and ascorbic acid, 100 mg. daily by injection, were given from October 28 to November 2.

The disease seemed to be an acute hepatitis developing in a case of pulmonary tuberculosis. The question arose whether it was due to a toxic effect of P.A.S. on the liver in a susceptible person or to a coincidental infection by the virus of infective hepatitis or to some other infection.

It was thought unlikely to be infective hepatitis for the following reasons. (1) The patient had been in hospital 24 days before the onset of the malaise and pyrexia which seemed to mark the beginning of the illness. During this time there were no cases of infective hepatitis among the staff or other patients. (2) During the previous three months she had not been in contact with any jaundiced patient, nor received any injections, nor was there any evidence of chemical poisoning. (This information was taken from her relations after her death.) (3) In 1950 this hospital met with no epidemic of infective hepatitis: only a few sporadic cases were seen. (4) According to Tidy (*Synopsis of Medicine*, 1945) the blood in infective hepatitis shows a leucopenia with relative lymphocytosis, whereas the blood in this case showed a polymorphonuclear leucocytosis.

Weil's disease was considered, but was thought unlikely for the following reasons. It is acute in onset, with high fever, pains in the muscles, haemorrhages, albuminuria, and with casts and red blood cells in the urine. This illness came on gradually and in other respects also was unlike Weil's disease. Unfortunately the urinary deposit was not examined for leptospirae, while the more exact methods of diagnosing Weil's disease were not available.

In the M.R.C.'s report on the treatment of pulmonary tuberculosis with streptomycin and P.A.S. (*Journal*, November 11, 1950, p. 1073) the occurrence of rashes during P.A.S. treatment is mentioned, but not that of toxic hepatitis. However, Cuthbert (*Lancet*, 1950, **2**, 209) has reported the occurrence of jaundice, with an itching maculo-papular rash and pyrexia, in a case of pulmonary tuberculosis under treatment with P.A.S. The patient was very ill, but recovered. The total dosage appears to have been 800 g. There was evidence that the symptoms were due to idiosyncrasy to P.A.S. developing during the course of treatment. The resemblance between this case and that of Dr. Hurrell's is close—in both there was a rash and hepatitis. The dosage of P.A.S. before symptoms occurred was 270 g., and the total dose before the drug was stopped was 465 g. In Dr. Hurrell's case the total was 163 g.

It is difficult absolutely to exclude an infection, but in this instance P.A.S. was at least suspect.

I am grateful to the superintendent of the hospital, Dr. S. T. Wu, for permission to write about this case.

—I am, etc.,

D. LANDSBOROUGH.

General Hospital, Chuanchow, Fukien, S. China.

## Histoplasmosis in England

SIR,—The answer to "What is Histoplasmosis?" in "Any Questions?" (February 3, p. 261) prompts me to record an unusual case of infection by *Histoplasma capsulatum* in Kent.

A man aged 35 years who had never been outside England was submitted to interval appendicectomy in January, 1947, following several attacks of subacute appendicitis. The appendix was thickened but not inflamed, and bound down by adhesions in the retrocaecal position. Convalescence was uneventful and the patient was discharged on the eighth day. Section of the appendix showed chronic inflammation and patches of fibrosis.

Six weeks after discharge the patient was referred back to me with a lump in the right iliac fossa. This looked and felt like a cold abscess. Investigation showed no evidence of tuberculosis in chest, spine, etc. Barium enema showed normal caecum displaced by the abscess. Blood count showed 8,000 white cells/c.mm., but normal differential count. Urine and stools were normal, though he had had diarrhoea.

Eventually, as the abscess appeared to be pointing in the right flank, it was incised. The cavity was about the size of a tennis ball and contained pus. This was dirty greyish-white in colour and contained sloughs and small greyish granules, similar in all respects but colour to actinomycotic pus. Microscopic examination showed the presence of *Histoplasma capsulatum*.

The wound healed rapidly with the establishment of free drainage and regular washouts with acromine, and the patient was discharged in three weeks. Since then there has been no recurrence.

The formation of a localized abscess six weeks after appendicectomy suggests that the infection originated in an infected appendix, despite the fact that no evidence of mycotic infection was noticed at its routine histological examination. As the barium enema showed no abnormality of the caecum other than its displacement by the abscess it can be assumed that the original infection was localized to the appendix.

The origin of the infection in a patient who had never been out of England is difficult to explain, but I have seen one case of histoplasmosis of lungs following a visit to Ireland, where this infection is known to occur—possibly spread from the U.S.A. Perhaps the fungus is now to be found in England, and the possibility of an increase in the number of cases of histoplasmosis there should be borne in mind, particularly in atypical chest diseases when the milder form of *Histoplasma capsulatum* infection may closely simulate tuberculous infiltration in its early stages, and later may even lead to patches of calcification. Cavity formation fortunately seems to be uncommon, even in the U.S.A., where this mild form of pulmonary histoplasmosis occurs sporadically.—I am, etc.,

Port Elizabeth, South Africa. C. B. LIMERICK.

## "Family Doctor"

SIR,—If *Family Doctor* is to succeed in "making life fuller, healthier, and happier" (March 17, p. 571) its staff should not be influenced unduly by the findings of the Metropolitan Life Insurance Company of New York. This excellent company doubtless knows the price of everything, but it would not presume to assess the value of anything—least of all of "informing the public of the warning signs of certain diseases." Conversely, your new journal should aim to determine the value of education to the individual in terms of freedom from worry regardless of the price to the scientists in terms of satisfaction.

It is invidious to quote from an excellent scientific article in your own journal (August 19, 1950, p. 431), but the following statement was made on the subject of the early diagnosis of what is still an incurable disease, "This . . . cannot be achieved, however, until disseminated sclerosis is made known to the general public. . . . Unless the lay public are taught to appreciate the potential significance of such symptoms as temporary weakness in a limb, transient dimness of vision, and diplopia the latter part of Buzzard's criticism . . . must remain justified." If such sentiments are to be translated into your new Popular Health Journal, I am afraid it will be neither popular with the family doctor nor healthy to his patients. The former will have his surgery further augmented with cases of disseminated neurosis, and those of the latter who do in fact suffer from the genuine disease will be forcibly informed in print that they are suffering from more than "a type of neuritis." What this can mean in pain and suffering and loathing has been expressed already in the *Diary of a Disappointed Man*, by W. N. P. Barbellion.

There is an old quotation, "I will deprive men of the foreknowledge of death which they possess at present. This power Prometheus has received my orders to take from them." It must be no part of *Family Doctor's* duty to reverse this process. This danger can be averted only if

your excellent new venture is inspired and written by the real family doctor and not by your usual contributors, the statistician and the diagnostician. It is so easy to debase the art of medicine into a sport in which all wish to excel in the brilliance of their own shots, and it is tempting to encourage potential patients to fly within range. But though we may level a diagnosis for fun, the patient suffers in earnest. Those of us who work in hospitals may forget this, but the real family doctor never does. I hope, therefore, that the Editor will be guided by those who regard the person as more important than the disease. Medicine is indivisible and Early Diagnosis is not enough.—I am, etc.,

Liverpool. JAMES ARKLE.

### Telling the Public of Health

SIR,—I would like to express my whole-hearted congratulations and thanks to Dr. Israel Gordon (March 24, p. 611) for producing such a useful and applicable article on "The Healthy Child." As so much of the general practitioner's work is in dealing with healthy people who think they are unhealthy, would it not be an excellent thing for those responsible for the training of medical practitioners to produce a small work on the "Healthy Human Being," under the aegis of Dr. Gordon, if he agrees—and, quite as important, for the Editor of *Family Doctor* to produce a version for the general public?

At the moment in our popular press, radio, and television there is far too much stress on disease, and it seems to me that it would be much better for the mental health of the population at large if we continually stressed the comparatively low incidence of disease among the population rather than the prowess and skill of the experts in dealing with comparatively rare conditions. To illustrate my point, I am continually telling my patients with throat conditions that I have not seen a positive diphtheria swab during four years of practice in an average-sized practice in suburbia. I may also have been singularly fortunate, but all my cases of poliomyelitis have been query or abortive; but consider the vast amount of mental agitation and worry that there has been during this time among many of my patients who have read all about these conditions in the popular press. The right perspective is impossible for the lay public to gain in matters of disease, and can we altogether blame the anxious mother who reads an article on poliomyelitis in the press by an undoubted authority on the subject and, petrified with fear because her child subsequently develops a cold with pyrexia and a slight sore throat, rings up her doctor to confirm her diagnosis? She has not seen the thousand similar cases her doctor has seen for every case of poliomyelitis which starts in the same way. This, however, is not usually stressed sufficiently by the propagandists of knowledge of disease, and, even if it were, it would not bring about the same conviction as that of years of experience in dealing with disease.

Therefore I feel that a swing over to prevention of disease and keeping the body fit by natural means would be a great step forward. How many of us, for instance, in this civilized era have anything like the right amount of exercise or fresh air that we should have? And unfortunately, thanks to the difficulties in obtaining the right sort of foods, our ideas on what constitutes the right diet have gone sadly awry.

Similarly, in the question of mental health in the present day too much stress seems to be placed on the abnormal rather than what is normal and usual. Young married couples, for instance, marry with the shadow of possible divorce hanging over them because they read so much about unhappy marital relationships. The problem and delinquent child is so much in the minds of young mothers that the slightest deviation in their own child tends to make them turn to the child psychiatrist rather than adopt ordinary means to combat the slight differences between the personality of their own child and that of the average child. I have indeed several patients who have worried themselves into a state of neurosis to the extent of thinking that they are actually going mad because of a superficial knowledge of psychology gained from the lay press. I am dealing at this moment with a victim of a stage stunt carried on by a hypnotist.

By all means let the intelligent person have access to knowledge about disease, but for the greater part of the population surely we would be better using our all-too-scarce lay press columns trying to promote positive health. I am quite sure that the efforts of Prunella Stack, whose tragic loss we all regret, were of much more value to the community than the daily outpourings of the disease propagandists.—I am, etc.,

Wembley, Middlesex. M. E. ARNOLD.

### Chicken-pox and Herpes Zoster

SIR,—In July, 1942 (*Journal*, **2**, 60) you published a note from me describing a case of varicella developing after contact with a case of herpes zoster. Since then I have come across similar cases occasionally, but a recent one is unique in my experience. On February 11 a woman aged 60 developed herpes zoster in the area of the eighth left dorsal root. On February 24 a daughter aged 30 developed varicella and on February 27 a second daughter aged 28 developed varicella, and on February 28 a third daughter aged 21 also developed varicella. None of the daughters had apparently been varicella contacts, and from the dates quoted above it seems certain that their infection was entirely due to contact with the mother's herpes zoster.—I am, etc.,

Stoke-under-Ham, Somerset. S. L. BRIMBLECOMBE.

### Behaviour of Blood Eosinophils

SIR,—We were interested to read Professor J. M. Yoffey's paper (March 31, p. 660) and your leading article (March 31, p. 684). You refer to Randolph and Rollins's finding that after prolonged administration of A.C.T.H. the fall in the peripheral eosinophil count may become less marked and may even disappear. We have found some evidence of this "escape phenomenon" in patients receiving electroconvulsive therapy, but not in patients who have a daily hypoglycaemic coma induced by insulin. In the latter we have noted, in about one-half of the cases, a continuous rise in the morning eosinophil count (total wet count, Randolph's stain), this count being taken at 10 a.m. in patients who were given an injection of insulin at 7 a.m. As the eosinophil count of the same patients showed a fall of over 50% in the post-stress period (count taken four hours after arousal from coma), we were interested to see whether their bone marrow showed signs of increased activity. We found no significant increase in the eosinophil bone marrow cells of these patients, a finding which confirms Professor Yoffey's earlier observation that A.C.T.H. and cortical extracts do not significantly increase the eosinophil cells of the marrow of guinea-pigs.

We feel justified in drawing the conclusion that there is no evidence of a re-entry of eosinophils into the bone marrow at the time when the peripheral eosinophil count is low, and that the behaviour of the eosinophil cell may differ in this way from that of the lymphocyte cell observed by Professor Yoffey in experimental animals. The fact that there appears to be no increase in the number of bone marrow eosinophil cells is not necessarily an indication that bone marrow activity has not been stimulated by a patient's exposure to stress. It may only indicate that the rate of production of eosinophils does not outstrip the rate of their passage into the general circulation. This supposition is supported by the observation that there is a gradual rise in the peripheral eosinophil count of some of these patients, whose granulocytes also show immaturity, which indicates a considerable degree of bone marrow stimulation.—We are, etc.,

F. MACKENZIE SHATTOCK.
J. MUNRO SHERRIFF.
LORNA P. MICKLEM.
ANNA STRAUTMANIS.

Arlesey, Beds.

### Death in Defectives

SIR,—The cause of death in mental defectives can occasionally be puzzling and obscure, requiring notice to the coroner and a necropsy to determine the precise nature of the terminal illness.

In this particular instance the patient was a single woman of 42, whose defect was of sufficient mildness for her to remain at home with her parents. Every month for 11 years she called for her panel certificate, and during the whole of this time remained and appeared physically fit, taking her daily walk in all weathers, winter and summer alike, without hat or coat.

Four days before death she was noticed to be somewhat listless, but did not complain or stay in bed; neither did she or her parents think it necessary to send for me. At 4 a.m. on the fourth day she was given a dose of medicine for a cough which had developed. Four hours later she was found to be dead.

At the post-mortem examination a state of acute general peritonitis was discovered, with 2 to 3 pints of purulent fluid in the pelvis. The inflammation had arisen from an appendix which had reached the gangrenous stage, and this was clearly the cause of death.

Although the oddities in her outward behaviour were noticed to be comparatively mild in character, the disturbances in her mentality were probably profound, if the apparent disregard of the pain she must have endured is to be considered as a guide to the severity of her long-standing complaint.—I am, etc.,

Blakeney, Glos. J. M. ASHTON.

### Vitamin C and the Common Cold

SIR,—In view of the evidence which has accumulated abroad since 1940, it is surprising that little attention has been paid in this country to the resistance that may be gained to the common cold and its complications by adequate quantities of ascorbic acid. This may be due, first, to the inconclusive results of the investigation carried out in Britain by Glazebrook and Thomson[1] in which the administration of 50 mg. daily led to no significant decrease in the number of colds or of tonsillitis, but did somewhat reduce the average period of illness; secondly, to the difficulty that various authorities have had in reaching agreement on the optimum daily intake of ascorbic acid.[2]

The incidence of scurvy is associated with prolonged and gross deficiencies of ascorbic acid,[3] and occurs at a level, less than 10 mg. daily for adults, which is far below "saturation level": with guinea-pigs, this level is less than one-fortieth of saturation level.[4] Sub-optimum levels are not easy to detect clinically; further, as abnormally high demands on ascorbic acid are made by variables such as physical effort, fever, etc., it is apparent that no single figure for the daily requirement is likely to suit all individuals at all times. This is as likely to vary according to circumstances as does that of common salt.

Completely consistent results between various experiments, even though well planned and controlled, are therefore not to be expected. However, there are now various reports showing a favourable effect on resistance to infection with daily doses of 90 mg. or more. The controlled investigation by Oskam on 392 factory workers in Holland in 1942 showed beneficial results from 90 mg. (after previous saturation): a similar test by Scheunert[5] on a total of over 2,000 German factory workers divided into groups of 240–380 showed a marked fall in illness over a period of eight months in 1942–3 with 100 or 300 mg. daily—a benefit not found with 20 or 50 mg. Related to these results but without controls are the prevention or amelioration of colds by relatively large doses of the order of 1 g. in cases which have not received additions to the ascorbic acid in the diet. Thus Wagner claims to have reduced the incidence of influenza in the Faroes; and Markwell[6] in Australia, after wartime experience of 1 g. doses on wound-healing, has applied the same technique with success to the abortion of colds. His report (which covers over 100 cases) states that with this massive dose, taken as soon as a cold is felt to be present, the cold is frequently but not always dispersed within a few hours. In almost all cases the after-effects and complications to which the common cold so often gives rise were non-existent after ascorbic acid treatment. The cases, admittedly limited, of which we have had personal experience over the last four winters are in general agreement with the above reports: for example, resistance to infection with daily doses (over and above that in the diet) of 50–100 mg. in the case of children.

We suggest that controlled trials along the lines of those with antihistamines (August 19, 1950, pp. 425, 430) should be carried out in this country so that first-hand information be obtained. We believe that, unlike the outcome of the antihistamine trials, the results may show that considerable benefits can arise from ascorbic acid treatment given in sufficient quantities at the right time.—We are, etc.,

JOHN M. FLETCHER.
Didcot, Berks. ISABEL C. FLETCHER.

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### Festival at Worcester

SIR,—Intending visitors to the first Sir Charles Hastings Memorial Festival, to be held on May 30 at Worcester, may like to know that hospitality is offered by the members of the Worcester and Bromsgrove Division to anyone who wishes to stay the Tuesday or Wednesday night in Worcester. Dr. C. Mackie, The Lower House, Stourport, has kindly offered to arrange accommodation, and any inquiries should be addressed to him.

For the convenience of visitors free car-parking close to the cathedral and the Worcester Royal Infirmary has been arranged, and all those attending will receive with their tickets of admission full details of the programme for the day (and see *Supplement*, April 14, p. 151). It will include a map of Worcester, and in addition the routes from the city boundary will be signposted. May I remind intending visitors that application for tickets should be made to Dr. M. P. Martin, 109, Laugherne Road, Worcester, enclosing remittance?

On behalf of my Division I cordially invite members of the Association to the Festival with confidence that they will spend an enjoyable day.—I am, etc.,

W. D. STEEL,
Chairman, Worcester and Bromsgrove Division.

## POINTS FROM LETTERS

### Medicine by Television

Dr. J. D. THOMPSON (Hampstead, N.W.3) writes: I understand that the *Journal* has as yet appointed no T.V. critic, and yet the profession seems to be well established on the television screen. Although one hesitates to make oneself a self-appointed critic, the experience of a dreary wet evening—a pre-Budget one at that, and a dreary performance on the screen to present *A Hundred Years of Medicine*—makes one feel that you should appoint a little space to criticism. No professional T.V. actors these, with suitable pseudonyms to present the epic, but some hard-working stars of the medical profession appeared under the lights. May I say here that they will shine more brightly in their own profession than they ever will as T.V. artists? Some were under-rehearsed and the make-up of most of them was either patchy or non-existent. A T.V. actor should not have to read his lines, nor would he neglect to attempt to put as much glamour into his appearance as the part would warrant. . . . If a programme of this sort must be presented to the viewers, cannot we have some light relief in the form of an odd song or two, as is done in *Country Magazine*? The only relief in this programme was in a short dance given by some diplococci on a slide before they were all too soon swept off stage by one of the sulphonamides. . . . Perhaps it would be better to leave the stage, the screen, and Alexandra Palace to professionals.

# Obituary

## A. S. BLUNDELL BANKART, M.Ch., F.R.C.S.

Mr. A. S. Blundell Bankart, consulting orthopaedic surgeon to the Middlesex and Royal National Orthopaedic Hospitals, died suddenly in London on April 8 at the age of 71.

Arthur Sydney Blundell Bankart was the only son of the late Mr. James Bankart, F.R.C.S., of Exeter, who was formerly a demonstrator of anatomy at Guy's Hospital. Born in 1879, Arthur Bankart was educated at Rugby School, Trinity College, Cambridge, and Guy's Hospital. He qualified in 1906, graduated B.Ch. in 1907, became a Fellow of the Royal College of Surgeons in 1909, and proceeded to the Mastership of Surgery in 1910. At Guy's he was successively house-surgeon, out-patient officer, clinical assistant, tutor, and surgical registrar, before entering consulting practice. His interest was at first divided between orthopaedic surgery, children's surgery, and neurosurgery. His appointment as registrar at the Royal National Orthopaedic Hospital led to his election to the staff of the hospital in 1913, and he held this post until 1947, when he joined the consulting staff of the hospital. Because of pressure of work he soon had to give up the post of assistant surgeon to the Belgrave Hospital for Children, but he continued as assistant surgeon to the Queen's Hospital for Children from 1912 to 1920, and thereafter was consulting surgeon to the hospital. He was also surgeon to the Hospital for Epilepsy and Paralysis, Maida Vale, from 1912 to 1934, before joining the consulting staff. In 1921 he was appointed orthopaedic surgeon at the Middlesex Hospital: from a very small beginning he built a large and important department of orthopaedic surgery at the hospital, being at a later stage assisted in the task by Mr. Philip Wiles. Bankart remained on the active staff of the Middlesex Hospital until 1946 and of the Royal National Orthopaedic Hospital until 1947. In addition to all this important hospital work he had a large private practice as a consultant orthopaedic surgeon.

Mr. Charles Gray writes: Bankart played a major part in the development of orthopaedic surgery in this country. He was one of the pioneers who promoted and sustained the specialty, and he made important contributions in numerous publications to the study of some of its problems. Special mention should be made of his work on recurrent dislocation of the shoulder, on tuberculosis of the hip, spinal arthritis and sciatica, and on manipulative surgery. He had the gift of clear and logical thought, which he expressed in beautiful prose. His writings are models of compact and perfect English. It is a remarkable fact that he wrote without correction, the first being nearly always the final draft, and ready for the printer without the alteration of a single word.

In his assistants he inspired respect and deep affection. He was a tireless worker and drove everyone hard in a round of enjoyable work, performed with astonishing punctuality and unfailing good humour. He always kept complete control of himself and never raised his voice in anger. Everything was done quietly, quickly, and efficiently. He loved the operating theatre and always enjoyed the long lists which were a regular feature of his work at the Middlesex Hospital. Bankart himself was a pupil of Arbuthnot Lane, of whom he spoke often with admiration and respect. He embellished and extended Lane's technique and operated with the most remarkable skill and precision. Technical problems were carefully worked out beforehand in his workshop at home with models and drawings. This practice, his natural dexterity, and his complete grasp of mechanical problems were the basis of his great success as an operator. He did not give much time to formal teaching, seldom lecturing and showing no inclination for systematic exposition in the wards or out-patient department.

He was upright, loyal, and courageous. He was also shy, and this gave an appearance of sternness and reserve which partially concealed a generous and kindly character. He was modest, and there was not the slightest trace of meanness or malice in his nature; but he despised incompetence and loathed pretence, and this was the basis for an occasionally critical comment. His death at the age of 71 removes a fine man and an outstanding surgeon.

P. W. writes: The death of Bankart is a sad loss to orthopaedic surgery, to which he contributed so much, but a great deal will be written about this elsewhere. It is to Bankart the man that I want to pay tribute, for he was shy, and few of his colleagues knew him really well. A man of outstanding intellect, he was a connoisseur of life and loved to savour its good things. He liked fine men, fine furniture, and fine wine, and had little use for mediocrity. He respected tradition but not dogma, and his integrity was such that he would tolerate no compromise with the truth. In his work—his work was his great love—he set his course and followed it without fear however unconventional it might be. Bankart was a friend above price. There are many whom he helped, but in so unobtrusive a manner that they were often unaware of what he had done. I myself owe more to him than I can easily say; he took me as a young man and taught me his craft, he made my path easy and encouraged me on the way. His death is a grievous loss, and he will be mourned wherever surgeons meet.

Mr. A. Rocyn Jones writes: The passing of Blundell Bankart removes one of the most outstanding of orthopaedic surgeons and one to whom a great debt was due for his contributions to orthopaedic surgery and for the part he played, in his own quiet way, in teaching young colleagues, many of whom are scattered all over the world. At Guy's Hospital he came under the influence of Arbuthnot Lane when that great surgeon was introducing internal metallic splinting of fractures and evolving the so-called "no-touch technique" in bone surgery. Indeed, Bankart was one of the first to spread that procedure to other clinics. He worked rapidly but neglected nothing, in either his clinical examinations or operations, and his opinion was much sought after by his colleagues. Through his attachment to Maida Vale Hospital he operated a great deal on the brain and spinal cord before neurosurgery had developed into a distinct specialty. At the Orthopaedic Hospital he achieved a reputation for his success in the treatment of congenital dislocation of the hip and also of clubfoot, for which he introduced silk ligaments to maintain correction. He was the first to introduce Stoffel's operation for spastic paralysis. He was a highly skilled manipulator and wrote a book on manipulative surgery which did a great deal to convince the profession, if not the public, that the art of the bone-setter was not unknown to orthopaedic surgeons. In 1923 he published in the *British*

*Medical Journal* a preliminary account of the pathology of recurrent dislocation of the shoulder and of his operation to cure the condition. A more elaborate description with illustrations of the operation appeared in the *British Journal of Surgery* in 1938. This operation has received world-wide acceptance and is likely to preserve his memory permanently. His colleagues and pupils will remember him with gratitude and affection for his kindness and his readiness to help them by his experience. They will recall that slim, pale figure of ascetic appearance, rather shy and with a soft, slightly husky voice.

## ROBERT BROOM, M.D., F.R.S.

Dr. Robert Broom, whose zoological and palaeontological studies in South Africa brought him international fame, died in Pretoria on April 6 at the age of 84.

Robert Broom was born in Paisley, where his father was a shawl designer. He was educated at Hutcheson's Grammar School, Glasgow, and the University of Glasgow, where he became assistant to the professor of chemistry. He graduated B.Sc. in 1887 and M.B., C.M. in 1889. Three years later he went to Australia to practise, and in 1897 moved to South Africa. From 1903 to 1910 he was professor of zoology and geology at Victoria College, Stellenbosch. In 1913 he gave the Croonian Lecture, entitled "The Origin of Mammals," before the Royal Society, to which he was elected a Fellow in 1920. During the first world war he served in the R.A.M.C. for two years and then returned to South Africa as a general practitioner. He held the appointment of district surgeon to the Herbert district until 1929, when he retired from medical practice. Three years later he took up practice again, but finally gave up medicine in 1934 on his appointment as Keeper of the Transvaal Museum, Pretoria.

We are greatly indebted to Sir Arthur Keith for the following appreciation: The death of Dr. Robert Broom brought to an end a career which has had no parallel in my time either in medicine or in science. He and I were born in the same year—1866; both of us took to anatomy, he under Professor John Cleland in the University of Glasgow, I under Sir John Struthers, who held the chair of anatomy in the University of Aberdeen. I had the better fortune in that I succeeded in being appointed to offices which permitted me to earn a livelihood and at the same time indulge myself in my anatomical hobbies. He, on the other hand, had to make his living by medical practice while he sought to unravel problems relating to the evolution of certain structures in the composition of the base of the vertebrate skull. From time to time he had to move his practice from one continent to another, selecting that which was most likely to provide him with the anatomical material he was in need of. In 1892, at the age of 25, he set up in practice in New South Wales, in order to study the skulls of the early mammalian forms to be found there. After five years in Australia, having married in the meantime, he moved to South Africa, where he put up his plate and began to collect reptilian fossil remains, which abound in the deposits of the Great Karroo. Between seeing patients he was busy describing unknown reptilian forms, many of them showing certain mammalian features. In 1932 he published a book with the title *The Mammal-like Reptiles of South Africa*, in which he summarized the results of 35 years of work in South Africa. That book marked a new chapter in our conception of the origin of mammals.

This 35-year period in South Africa was interrupted by various episodes which bring out Broom's love of independence—independence in what he thought and did. After six years in South Africa he was appointed professor of geology in the University of Stellenbosch, but after five or six years gave up the chair and went back to medical practice, and so recovered his freedom from the control of officialdom. Somehow his own freedom of expression put obstacles in his way, and continued to do so right up to the end. His mind moved quickly but impatiently; one might truly say he was the victim of convictions.

In 1932, having finished his book on the mammal-like reptiles, he broached another subject which at that time was comparatively new to him—the origin of man, particularly man's relation to anthropoid apes. He formulated his ideas in a book which appeared in 1933 with the title *The Coming of Man—Was it Accident or Design?* Broom believed in evolution, but was inclined to accept Lamarck rather than Darwin. The chief reason for the publication of this book was to vindicate Dart's claim that the fossil anthropoid skull found at Taungs in 1924 represented a form of ape more akin to man than to the other anthropoid apes of Africa, the chimpanzee and gorilla, whereas I, and most of my contemporaries, regarded the Taungs ape as a cousin of the chimpanzee.

Having published these two books Broom again settled to practise at Griqualand West, so that if further discoveries of anthropoid fossils were made he would be on the spot to see them. When thus employed there came to him in 1934 two wise statesmen, General Smuts and J. H. Hofmeyer, who persuaded him to give up practice and devote himself to the task for which he was so uniquely qualified. They had a post waiting for him in the Transvaal Museum, Pretoria—a post which he accepted and continued to hold until his death. Broom, when he went to Pretoria, was in his 68th year.

From 1924 until the time Broom took up his appointment no further trace of the fossil anthropoids of South Africa had come to light. He set to work to make this omission good. In 1936, while excavating a cave at Sterkfontein, near Krugersdorf, Broom uncovered a fossil skull which at first he believed to be the adult form of the Taungs anthropoid (that of an infant), but later decided that it represents a different genus. After the discovery at Sterkfontein fortune continued to smile on him, so that by 1946 (when he was in his eightieth year) his anthropoid collection had become so large and varied that, with assistance from Dr. Schepers, he devoted to its description a large memoir entitled *The South African Ape-men—The Australopithecinae*. Other discoveries followed the publication of this monograph, the most important being that made, again in the Sterkfontein cave, in August, 1947, when he dug out the pelvis of a female ape. That pelvis was modelled much more on human than on anthropoid lines; there could then be no longer any doubt that the South African anthropoids were adapted, as Dart had postulated, to life on the ground. Here Broom uncovered in a morning what I had been looking for all my life; but he dug—I only waited. At the time of his death he was busy preparing his new material in another monograph.

He was a lovable man, one who retained much of the boy in his nature, full of life, zest, and fun, intolerant only of the pretender.

## H. DE VERE STACPOOLE, L.S.A.

H. de Vere Stacpoole, who was a ship surgeon and general practitioner before he became a novelist, died at Shanklin in the Isle of Wight on April 12 at the age of 88.

Henry de Vere Stacpoole was born in Dublin, the son of a clergyman. He was educated at Malvern College and came to London to study medicine first at St. George's Hospital and later at St. Mary's. He qualified L.S.A. in 1891 and was in general practice for some years. An ardent traveller, he went on several voyages as a ship surgeon. In 1903 he published a monograph entitled "The Floor of the Sea." Shortly after the beginning of the century he decided to give up medicine altogether, and took to writing for a living. One of his first novels was *The Doctor*, which he himself thought was his best book. The most widely read of his novels, *The Blue Lagoon*, was published in 1910. Stacpoole wrote 63 books in all, among them several books of poems, including translations of Villon and Sappho. His autobiography, *Men and Mice*, appeared in 1942, and its successor, *More Men and Mice*, in 1945.

We are indebted to Mr. Alfred Noyes for the following appreciation:

Henry de Vere Stacpoole had a place peculiarly his own in modern literature. As a ship surgeon he acquired a great deal of material for the background of such stories as *The Crimson Azaleas*, *The Blue Lagoon*, and *The Street of the Flute Player*. But he was essentially an imaginative writer in the best sense of the word. He disliked the crude and superficial "realism" which is so often mistaken nowadays for reality. As one of the best of his contemporaries wrote, accuracy of detail and truth to general principles are nowhere more artistically important than in a work of pure imagination. His scientific training enabled him to follow this rule with great success, and gave his most romantic fantasies something of the philosophical quality of a parable. The titles of many of his books are in themselves very suggestive of this quality, *The Beach of Dreams*, for instance, and *The Pools of Silence*, the latter being a powerful indictment of certain happenings in the Belgian Congo. In addition to his novels he wrote a fascinating life of François Villon and translated many of his poems.

His Bonchurch garden was the subject of a delightful book of verse. Flowers and birds were his familiar friends, and he interested himself actively in the protection of sea-birds. One of the most characteristic of his Bonchurch poems, *Ghosts*, reproduces the very atmosphere of his garden and the drawing-room that opened upon it:

> Outside the far-off rooks make strife,
> Birds flit from tree to tree,
> Remaineth here the ghostly life
> Of birds in marquetry.
>
> Open upon the spinet stands
> A ballad, page on page,
> Once turned by who knows what white hands
> Of the Victorian age?
>
> All things remain just as they were,
> Mayhap the hearts to win
> Of people in the garden fair
> Who gaze, but come not in.

With his real scientific knowledge he detested the pseudo-modern attempts to turn literature and the arts into amateur dabblings in pathology. He knew that the special function of art was the revelation of beauty. His friends, among whom I was privileged to count myself, will miss him greatly.

## K. D. WILKINSON, O.B.E., M.D., F.R.C.P.

Professor K. D. Wilkinson, senior physician to the United Birmingham Hospitals, died on April 12, a few days before he would have attained his sixty-fifth birthday, when he was due to retire from the active staff.

Born at High Legh in Cheshire, the eldest of three sons of the Reverend H. C. Wilkinson, Kenneth Douglas Wilkinson was educated at Berkhamsted School and at Birmingham University, graduating M.B., Ch.B. in 1909. His student career was distinguished; he won the Richards Memorial Prize Essay and the Senior Prize in clinical medicine. He proceeded M.D. in 1912 and took the M.R.C.P. in 1914. After holding a number of resident hospital posts—he was house-surgeon to Jordan Lloyd at the Queen's Hospital and resident medical officer at the General Hospital under Robert Saundby—he was elected assistant physician to the Children's Hospital in 1913 and to the General Hospital in 1914. In 1925, on the death of James Russell, he became honorary physician. Throughout the 1914–18 war he served with the R.A.M.C.(T.), first with a south Midland field ambulance and later in casualty clearing stations and general hospitals; he was mentioned in dispatches and awarded the O.B.E. in 1918. With the late Professor George Gask he published in 1917 an important report on the treatment of penetrating gunshot wounds of the chest.

After demobilization Wilkinson soon became a busy hospital consultant with a considerable private consulting practice. He was an original member of the British Paediatric Association and of the Cardiac Society: in 1935 he delivered the Ingleby Lectures on rheumatism and the heart in childhood. Elected F.R.C.P. in 1929, he became Professor of Therapeutics at Birmingham University and an examiner at Cambridge, Manchester, and the Royal College of Physicians. His main interest was the study of disorders of the heart and circulation: he wrote many articles for textbooks and journals and he was cardiologist to the Birmingham City Hospitals.

During the last war he was regional consultant in medicine for No. 9 Region and group officer for Birmingham.

H. W. F. writes: Alert in manner and frank in speech, "The Wilk," as he was known to Birmingham men, recognized that hard work and continuous endeavour are essential for a successful career. He was not afraid in consultation to be dogmatic, nor in precept to be didactic. He possessed a good memory and was a very acceptable teacher who illustrated medical principles effectively from experience. For him life was vivid: he was acutely aware of the taste of things—whether sweet, bitter, salt, or acid. He enjoyed his work, his family, his friends, and his hobbies; and he knew quite well the things he did not like. The round of golf, the rubber of bridge, the telling of a story: these were performed effectively and enjoyed thoroughly. He was an early devotee of the radio, cinematography, and colour photography. He took special pains in his studies of the history of Birmingham and acquired a very interesting collection of pictures of old Birmingham and its worthies. The author of a history of the Birmingham Medical School, he produced last year a noteworthy volume founded upon extensive researches by the late

T. Whitmore Peck and himself about the family, the career, and the friends and surroundings of William Withering of Birmingham, discoverer of digitalis. This is the picture of an able and enthusiastic worker, but it would not be complete without mention being made of his sensitive and kindly, even sentimental, heart, which, however, he did not wear upon his sleeve. He had been in ill-health since 1945: having survived three coronary occlusions, he had resumed practice, only to be gradually overwhelmed by an even more relentless disease. His fortitude throughout so prolonged a strain on mind and body commanded widespread admiration and sympathy. Wilkinson was twice married: in 1916 to Miss Phebe Homewood, who died in the sad days of 1940, and to Dr. Agnes Crozier. He leaves a family of seven.

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Dr. NEVILLE AVORY EDDLESTONE died at the Royal Victoria Infirmary, Newcastle-upon-Tyne, on February 22, a few hours after being taken ill in a patient's house. He was 66 years old. Eddlestone graduated M.B., B.S. with honours at Durham in 1906, proceeding M.D. three years later. He was an outstanding student, being keen, efficient, conscientious, a regular prizewinner, and an excellent clinician. After holding resident posts at the Royal Victoria Infirmary, Newcastle—he was house-surgeon to the late A. M. Martin and house-physician to the late Professor Beattie—he decided to enter general practice, and settled in his home town after an assistantship at Maryport. In 1909 he succeeded to an old-established practice in Monkseaton and Whitley Bay and became one of the ablest and best-loved doctors in the district. Here he practised for 42 years, being in addition medical officer to Trinity House and the Prudhoe Convalescent Home. While taking little part in public life, he was devoted to his work and family. Of a most pleasing personality, cheerful, considerate, and with great clinical ability, his services were in constant demand. His relatively early death at the age of 66 was no doubt hastened by the hard work of the war years. Our deep sympathy is extended to his widow and daughter, who is a doctor.—F. C. P.

# Medical Notes in Parliament

### The Budget

In the course of his Budget speech on April 10 Mr. HUGH GAITSKELL explained that to keep the cost of the National Health Service within £400m. he proposed to charge approximately half the scale fee of all denture work and about half the cost of each pair of glasses. He said there would be no charge for children's spectacles, and expectant and nursing mothers would continue to receive free dental treatment; children would continue to receive free treatment in schools. Those for whom the charges meant hardship would receive payment in whole or in part from the National Assistance Board in the usual way. It was expected that the charges would produce about £25m. in a full year, but only about £13m. in 1951–2.

### Swiss Beds for British Patients

Replying on April 10 to Mrs. ALICE CULLEN, Mr. Hector MCNEIL said that Parliament would shortly be invited to consider legislation to provide for tuberculosis treatment abroad. For this year there would be from 150 to 200 beds in Swiss sanatoria for patients from Scotland, who would normally be those needing at least six months' sanatorium care but unlikely to require any major surgical operation. Treatment in Switzerland would be offered to anyone recommended for sanatorium treatment in the ordinary way, where on medical grounds this was considered appropriate by the responsible tuberculosis physicians.

In answer to a further question on April 12 Mr. HILARY MARQUAND said there would be beds for about 160 patients from England and Wales, and it was hoped to start sending patients to Switzerland in a few months' time.

### Employing the Elderly

Mr. J. R. BEVINS moved on April 13 a motion declaring that active steps should be taken by the Government to encourage the retention of the middle-aged and elderly in employment. He said the span of life was greatest in those employments where opportunities existed to continue work. In 1851 something like 1,000,000 men and women were over 65. In June, 1950, the number had risen to 5,400,000 out of a total working population of 23,000,000. If present-day mortality rates persisted the number would rise by 1977 to 7,300,000, whereas if mortality rates continued to fall it would rise to 8,200,000. If the present attitude to the elderly persisted, considerable man-power would be wasted and a burden would fall increasingly on the shoulders of the relatively young. The Ministry of Labour had ascertained that the rule of compulsory retirement applied to 26% of the white-collar staff and 15% of the manual workers in manufacturing, building, and transport. In local government the rule applied to 65% of all workers. In public utilities and finance it applied to 76% of the white collar workers and to 89% of the manual workers. He asked whether the retirement rule in Government departments was flexible or inflexible.

Mr. KENNETH THOMPSON said that, as an industrial medical service in various industries examined new entrants to decide what their physical condition was, there was no reason why employees should not be examined at 55, again at 60, and again at 62 or 65 that their physical condition might be assessed and advice given on the life they should lead. The medical adviser could inform the firm of the kind of employment for which the individual was most suitable.

Mr. A. C. MANUEL said that if labouring classes in heavy industries were persuaded by financial inducement or patriotic appeal to stay on after retirement age it would damage their physical health and might reduce their expectation of life. They should encourage old people to stay on in industries where their employment was light.

Mr. TOM BROWN declared that only about 700,000 industrial workers would be affected by the motion. The Government should not apply compulsion but leave the extension of working life to the wish of those concerned.

Sir PETER BENNETT said the real problem was that of the prematurely aged—of the people who were aged at 50 and had to be helped along till they reached 60 or 65.

Mr. P. DAINES remarked that, when unemployment had been rife, retirement was often a ticket to death. Retired engine-drivers had a staggeringly short period of life.

Mr. BEVERLY BAXTER said that men who had held high positions in the Navy, healthy and vigorous, were retired and in two or three years died. This death rate should be looked into.

Mr. F. LEE, replying for the Ministry of Labour, said the Government had no intention to compel people to remain in industry. The problem of retaining elderly people at work had lately been discussed with both sides of the National Joint Advisory Council, and he was assured of the full support of industry in taking any measures which might be necessary. Many people would have a happier old age if they continued longer in work. The two sides of industry had agreed to circulate through their constituent organizations a statement of the practical steps which would help elderly workers to stay on or to get fresh help.

Mr. VAUGHAN-MORGAN said that London Transport was now taking on men over 50 as drivers and conductors.

Mr. HARRY HYND suggested that there should be "Remploy" factories for older people as well as for the disabled.

The House agreed to the resolution moved by Mr. Bevins.

# INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles for the week ending March 31 (No. 13).

Figures of notified *cases* are for: (*a*) England and Wales (London included). (*b*) London (administrative county) (*c*) Scotland. (*d*) Northern Ireland. (*e*) Eire. Figures of *birth and deaths* and of *deaths* recorded under each disease are for: (*a*) The 126 great towns in England and Wales (London included). (*b*) London (administrative county). (*c*) The 16 principal towns in Scotland. (*d*) The 10 principal towns in Northern Ireland. (*e*) The 13 principal towns in Eire. A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, Northern Ireland, and Eire, the Ministry of Health and Local Government of Northern Ireland, and the Department of Health of Eire.

| Disease | 1951 Week Ending March 31 | | | | | 1950 Corresponding Week | | | | | 1942–50 England & Wales Corresponding Week | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (*a*) | (*b*) | (*c*) | (*d*) | (*e*) | (*a*) | (*b*) | (*c*) | (*d*) | (*e*) | Highest | Median | Lowest |
| Diphtheria | 46 | 3 | 16 | 1 | 2 | 67 | 5 | 17 | 2 | 4 | 793 | 478 | 67 |
| Deaths | 1 | — | — | — | — | 1 | — | — | — | — | | | |
| Dysentery | 999 | 147 | 212 | 18 | | 461 | 11 | 100 | — | 3 | 461 | 188 | 62 |
| Deaths | | 1 | | — | | | | | — | | | | |
| Encephalitis, acute | 4 | — | — | — | | 2 | — | — | — | — | 5 | 1 | — |
| Deaths | | — | | | — | | — | | | | | | |
| Erysipelas | | | 40 | 8 | 6 | | | 32 | 4 | 4 | | | |
| Food-poisoning | 88 | 9 | | — | | 29 | 8 | | 1 | | | | |
| Infective enteritis or diarrhoea under 2 years | | | | 12 | 15 | | | | | 16 | | | |
| Deaths | 17 | | 1 | — | — | 12 | | 4 | — | 4 | | | |
| Measles* | 31,268 | 2,360 | 336 | 131 | 104 | 6,307 | 118 | 285 | 360 | 93 | 22,183 | 10,783 | 2,282 |
| Deaths | | 4 | 1 | — | — | | | — | — | 2 | | | |
| Meningococcal infection | 58 | 3 | 19 | 2 | 3 | 36 | 5 | 10 | 1 | 2 | 180 | 74 | 30 |
| Deaths | | — | 3 | | | | 1 | — | | | | | |
| Ophthalmia neonatorum | 20 | — | 10 | — | | 56 | 4 | 13 | 1 | | 90 | 72 | 29 |
| Pneumonia, influenzal | 909 | 48 | 8 | 10 | 4 | 941 | 45 | 9 | 7 | — | 1,505 | 1,079 | 746 |
| Deaths (from influenza)† | 64 | 8 | — | — | 3 | 121 | 18 | 3 | 4 | 8 | | | |
| Pneumonia, primary | | | 231 | | | | | 167 | | | | | |
| Deaths | 289 | 40 | | 11 | 9 | 245 | 39 | | 8 | 14 | | | |
| Poliomyelitis, acute: | | | | | | | | | | | | | |
| Paralytic | 19 | — | 2 | — | — | 20 | — | 1 | 2 | 3 | 20 | 6 | 6 |
| Non-paralytic | 4 | — | | | | | | | | | | | |
| Deaths§ | 2 | — | | | — | 2 | — | | | — | | | |
| Puerperal fever | | | 3 | | | | — | 8 | | | | | |
| Puerperal pyrexia‖ | 62 | 2 | 4 | 2 | 1 | 82 | 8 | 8 | 1 | 1 | 168 | 141 | 82 |
| Scarlet fever | 918 | 61 | 143 | 24 | 61 | 1,749 | 116 | 220 | 105 | 80 | 2,450 | 1,361 | 1,115 |
| Deaths | | — | — | — | — | | | — | 1 | — | | | |
| Smallpox | — | — | — | — | | — | — | 21 | — | | | | |
| Deaths | | | | — | | | | | — | | | | |
| (1) Tuberculosis, respiratory | | | 171 | 13 | | | | 182 | 49 | | | | |
| (2) Tuberculosis, non-respiratory | | | 32 | 4 | | | | 27 | 2 | | | | |
| (1) Deaths | 152 | 31 | 35 | 7 | 17 | 188 | 29 | 29 | 7 | 20 | | | |
| (2) Deaths | | 4 | 3 | — | 4 | | 2 | 1 | 1 | 2 | | | |
| Typhoid fever | 7 | — | — | — | 3 | 1 | — | — | — | 2 | | | |
| Deaths¶ | — | — | — | — | | 1 | — | — | — | | 18 | 8 | 1 |
| Paratyphoid fever | 21 | — | 1 (B) | — | | — | — | — | — | | | | |
| Whooping-cough | 4,098 | 198 | 557 | 25 | 59 | 2,488 | 116 | 362 | 80 | 67 | 2,998 | 2,141 | 1,123 |
| Deaths | 4 | — | 3 | — | — | 3 | — | 2 | 2 | 1 | | | |
| Deaths (0–1 year) | 311 | 39 | 43 | 17 | 24 | 250 | 31 | 44 | 9 | 28 | 549 | 375 | 250 |
| Deaths (excluding stillbirths) | 5,826 | 910 | 691 | 152 | 209 | 5,348 | 810 | 612 | 130 | 260 | 6,101 | 5,090 | 4,677 |
| Annual death rate (per 1,000 persons living) | | | 14·0 | | | | | 12·3 | | | | | |
| Live births | 7,696 | 1,236 | 999 | 247 | 476 | 7,826 | 1,290 | 1,003 | 262 | 448 | 10,678 | 7 826 | 5,616 |
| Annual rate per 1,000 persons living | | | 20·2 | | | | | 20·1 | | | | | |
| Stillbirths | 199 | 30 | 29 | | | 181 | 18 | 25 | | | 285 | 219 | 181 |
| Rate per 1,000 total births (including stillborn) | | | 28 | | | | | 24 | | | | | |

* Measles not notifiable in Scotland and returns are approximate. † Includes primary form for England and Wales, London and N. Ireland. § The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, and London (administrative county), are combined. ‖ Includes puerperal fever for England and Wales and for Eire. ¶ Deaths from paratyphoid fever are combined with those from typhoid fever.

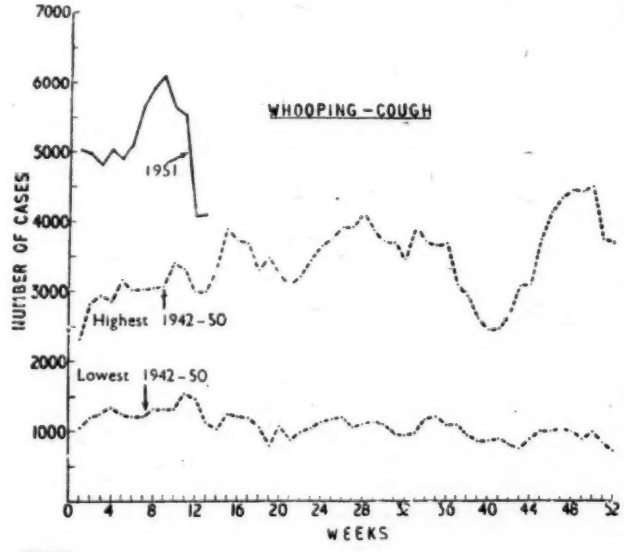
# Vital Statistics

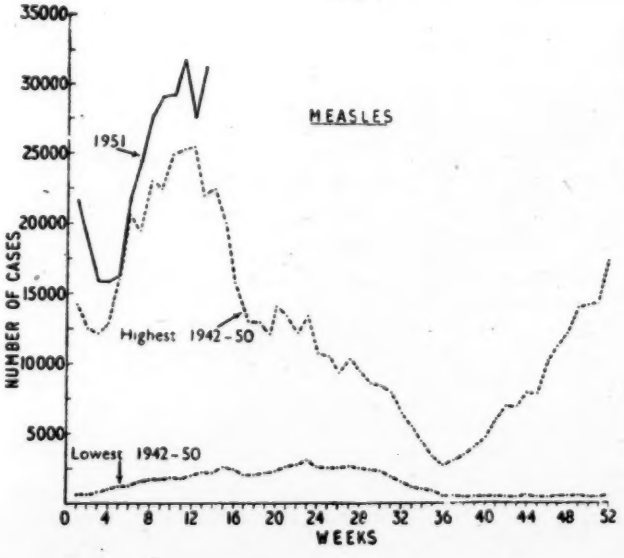
### Quarterly Returns for England and Wales

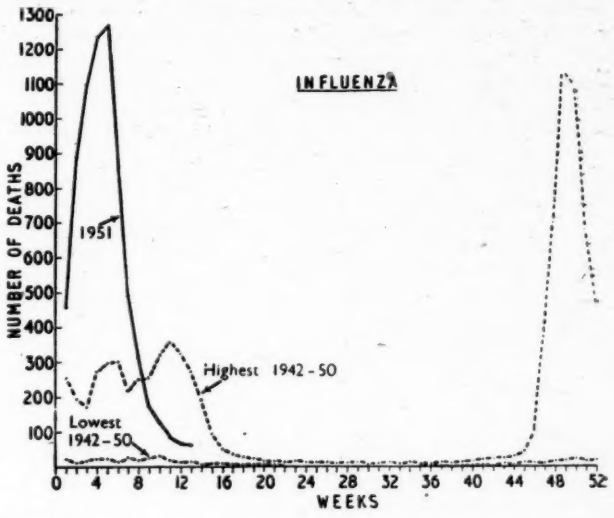
The birth rate during the December quarter of 1950 was 14.5 per 1,000 and was the lowest rate for any quarter since 1941. The infant mortality was 30.2 per 1,000 related live births; this was the lowest rate recorded in any fourth quarter, being 2.1 below the rate for the preceding December quarter. The general death rate was 12.3 per 1,000 of the population, being 0.7 above the rate for the fourth quarter of 1949; it was the highest rate for any December quarter since 1943. Deaths attributed to acute poliomyelitis numbered 201, compared with 330, 86, 71, and 373 in the four preceding quarters. The corrected notifications of acute poliomyelitis were 1,578 paralytic and 524 non-paralytic cases.

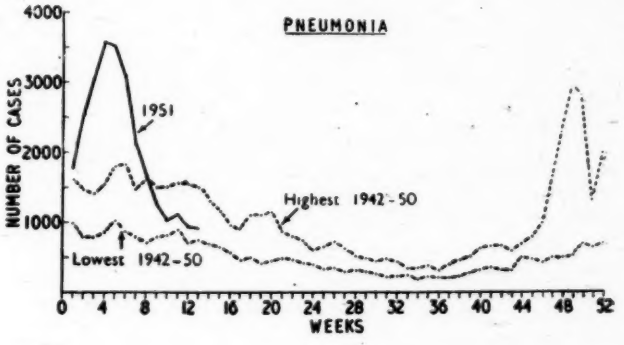
### Graphs of Infectious Diseases

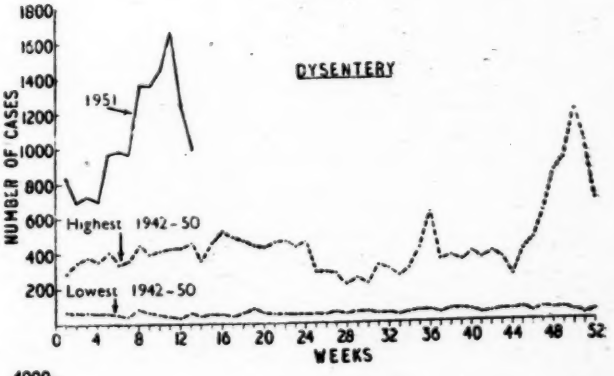
The graphs below show the uncorrected numbers of cases (deaths from influenza) of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1942–50 are shown thus - - - - - -, the figures for 1951 thus ————. Except for the curves showing notifications in 1951, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.

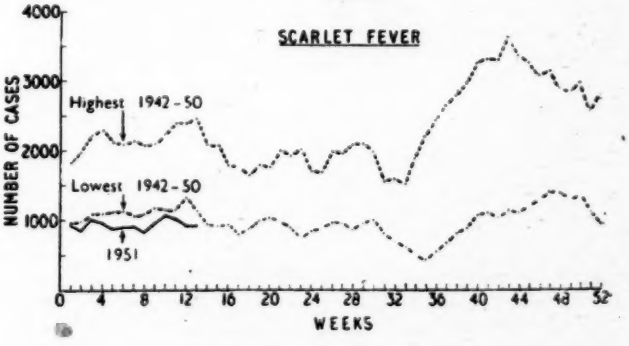



### Infectious Diseases

The only large departures from the trends of infectious diseases during the week ending March 31 were a rise of 3,455 in the number of notifications of measles and a fall of 257 in the notifications of dysentery.

Large rises in the number of the notifications of measles were recorded throughout the country. The largest increases were: Southampton 346, Middlesex 248, Kent 236, Yorkshire West Riding 230, Glamorganshire 228, Lancashire 209.

Cheshire 207, while the chief exceptions to the general trend were decreases in London 158 and Warwickshire 111.

There were 19 more notifications of whooping-cough than in the preceding week. The largest variations in the local trends were an increase of 84 in Kent and a decrease of 62 in London. No change of any size occurred in the local returns of scarlet fever. The chief feature of the returns for diphtheria was an increase of 6 in Staffordshire; the 8 cases in this county were all notified in Coseley U.D.

The notifications of acute poliomyelitis were 10 more than in the previous week. The largest returns were Warwickshire 5 (Birmingham C.B. 3, Coventry C.B. 2) and Norfolk 4 (St. Faiths and Aylsham R.D. 3). The largest returns for dysentery were London 147, Lancashire 103, Yorkshire West Riding 70, Lincolnshire 69, Middlesex 68, and Essex 66.

## Disease in First Quarter

During the first quarter of this year the incidence of infectious diseases in England and Wales has been generally very high. The numbers of notifications of measles have been large, and during the period February 24 to March 31 the number of notifications was from 2,269 to 6,330 above the previous highest return of March 24, 1945. The numbers of notifications of whooping-cough during the quarter have also been the largest since registration began, and during the period February 17 to March 17 they were higher than the previous highest level, recorded in 1941. The incidence of dysentery has also been the highest of recent years. Some of the large outbreaks of dysentery have persisted for several weeks. The notifications of diphtheria were the fewest ever recorded, and the weekly totals during the quarter varied from 30 to 51. The incidence of acute pneumonia was high, as might be expected during an influenza outbreak.

In the large towns the number of deaths from influenza was the largest for several years. The number of deaths from all causes was 12,267 to 37,510 above the number registered in the first quarters of the four preceding years. A further fall in the number of live births occurred, and the number was smaller than for any year since 1945, when 87,123 live births were registered in the first quarter.

A comparison of the returns for the first quarters of the last five years is made in the Table below:

| England and Wales | Number of Notifications | | | | |
|---|---|---|---|---|---|
| | 1947 | 1948 | 1949 | 1950 | 1951 |
| Scarlet fever | 15,527 | 23,348 | 16,087 | 24,802 | 12,088 |
| Whooping-cough | 27,922 | 35,034 | 37,221 | 23,619 | 66,865 |
| Diphtheria | 2,832 | 2,466 | 1,523 | 955 | 572 |
| Measles | 165,895 | 88,489 | 201,140 | 54,568 | 311,709 |
| Acute pneumonia | 15,500 | 10,969 | 17,147 | 13,720 | 26,536 |
| Meningococcal infections | 1,100 | 629 | 479 | 536 | 662 |
| Acute poliomyelitis | 126 | 417 | 245 | 512 | 339 |
| Dysentery | 931 | 2,100 | 886 | 3,938 | 13,995 |
| Typhoid and paratyphoid fevers | 98 | 103 | 100 | 154 | 149 |
| **Great Towns** | | | | | |
| No. of influenza deaths | 1,335 | 272 | 2,278 | 1,088 | 7,157 |
| No. of deaths from all causes | 92,759 | 67,516 | 84,957 | 77,311 | 105,026 |
| No. of live births | 130,468 | 108,621 | 101,948 | 98,022 | 94,022 |

## Bus Conductors and Poliomyelitis

The high incidence of poliomyelitis among children of bus conductors is discussed by Dr. H. Kenneth Cowan, Essex County Medical Officer of Health, in his report for the year 1949. In that year 345 confirmed cases of acute anterior poliomyelitis and acute polio-encephalitis were notified in Essex. In studying various aspects of the outbreak (in collaboration with Dr. Allan McFarlan, of the Department of Medicine at Cambridge University) the occupation of either the patient or the chief wage-earner of the household was obtained in 231 cases. An unexpectedly high number of cases (10) were found to be children of bus conductors. There were only 8 bus conductors concerned, because in two cases two children of the house were affected. This unusually high incidence is considered to be statistically significant. The most likely explanation is thought to be that the fathers, being in contact with large numbers of people, including children, became carriers and passed the disease on to their children.

Another conclusion of this study, which it is said should be accepted with reserve, is that there was a significantly higher proportion of poliomyelitis cases among the families of agricultural workers and a significantly lower proportion among the professional and managerial group.

## Alcoholism in Scotland

Discussing the problem of alcoholism in Scotland in the *Health Bulletin* of the Department of Health for Scotland (April, 1951), Dr. W. Robertson gives some figures showing deaths from alcoholism and deaths from cirrhosis of the liver by age groups in Scotland this century. The following Table is compiled from the data that he provides:

| Period | Deaths from Alcoholism | | Deaths from Cirrhosis of Liver | |
|---|---|---|---|---|
| | Males | Females | Males | Females |
| 1900–4 | 891 | 535 | 722 | 436 |
| 1905–9 | 698 | 437 | 698 | 472 |
| 1910–14 | 538 | 322 | 776 | 465 |
| 1915–9 | 359 | 227 | 569 | 356 |
| 1920–4 | 302 | 124 | 517 | 287 |
| 1925–9 | 194 | 65 | 560 | 261 |
| 1930–4 | 107 | 34 | 493 | 268 |
| 1935–9 | 101 | 36 | 580 | 334 |
| 1940–4 | 112 | 31 | 456 | 254 |

He points out that caution is necessary in interpreting figures of this kind. He concludes that the mortality ascribed directly to alcoholism, and in rather less degree the prevalence as reflected by the frequency of convictions for drunkenness (for which he also gives figures), have shown considerable improvement since the beginning of the century. This improvement applies to each sex, every age period, and every geographical region of Scotland. He does not discuss whether cirrhosis of the liver is attributable to the consumption of alcohol.

## Drink and Tobacco

What people in the United Kingdom have spent in the years 1946–50 on certain consumers' goods is analysed in a recent Treasury publication.[1] The following table shows the personal expenditure (in millions of pounds revalued at 1948 prices) on alcoholic drinks and tobacco, together with "All Expenditure" for comparison.

| | 1946 | 1947 | 1948 | 1949 | 1950 |
|---|---|---|---|---|---|
| Alcoholic drink: | £m. | £m. | £m. | £m. | £m. |
| Beer | 571 | 541 | 525 | 508 | 521 |
| Wines, spirits, cider, etc. | 213 | 239 | 237 | 220 | 240 |
| Tobacco: | | | | | |
| Cigarettes | 779 | 674 | 642 | 621 | 635 |
| Pipe tobacco, cigars, and snuff | 140 | 124 | 131 | 130 | 122 |
| All expenditure | 7,946 | 8,187 | 8,204 | 8,360 | 8,610 |

In the four years 1946–9 expenditure on both alcoholic drinks and tobacco gradually declined, while total expenditure increased. In 1950 total expenditure continued to increase, while expenditure on alcoholic drinks and tobacco also rose. Among the various categories of consumers' goods, expenditure only on food, and on clothing in some years, exceeded that on either alcoholic drinks or tobacco. The categories of goods on which less was spent include fuel and light; rent, rates, and water charges; household goods; travel; and durable household goods.

[1] *National Income and Expenditure of the United Kingdom, 1946-50* (H.M.S.O., 1s. 9d.)

### Road Accidents

Road casualties in February totalled 13,027, including 342 deaths. Compared with February, 1950, there was an increase of 8 in the killed and of 978 in the injured. Weather conditions, particularly ice, frost, and snow, were the primary cause of 570 accidents, compared with 234 in the corresponding month last year.

### Week Ending April 7

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 843, whooping-cough 4,009, diphtheria 48, measles 28,800, acute pneumonia 799, acute poliomyelitis 15, dysentery 846, paratyphoid fever 27, typhoid fever 8. Deaths from influenza in the great towns numbered 49.

## Universities and Colleges

### UNIVERSITY OF LONDON

Joseph Harold Sheldon, M.D., F.R.C.P., has been elected a Fellow of King's College. Dr. Sheldon is Director of Medicine and senior physician at the Royal Hospital, Wolverhampton, and Lecturer in Clinical Medicine in the University of Birmingham. He was appointed a Hunterian Professor of the Royal College of Surgeons of England in 1928, and in 1934 he delivered the Bradshaw Lecture before the Royal College of Physicians of London.

The following have been appointed, or nominated for appointment or reappointment, as representatives of the University on the governing bodies indicated in parentheses: Professor J. M. Mackintosh (Council of Management, Slough Industrial Health Service, Ltd.); Mr. A. C. H. Bell (Training College for Midwife Teachers, New Malden).

Professor H. A. Krebs will deliver four lectures on "Energy Transformations in Living Matter" in the physiology theatre of University College, Gower Street, London, W.C., on Thursdays, April 26 and May 3, 10, and 17, at 4.45 p.m.

Three lectures on "Obstetric Trends in a Changing Society" will be delivered by Professor Dugald Baird at the London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., on Wednesday, Thursday, and Friday, May 2, 3, and 4, at 5.30 p.m.

Professor G. Liljestrand (Karolinska Institutet, Stockholm) will deliver a lecture on "Studies on the Regulation of Arterial Blood Pressure" in the physiology theatre of University College, Gower Street, W.C., on Thursday, May 10, at 5.15 p.m.

An open lecture on "Monkeys and Agriculture" will be delivered by Professor S. Zuckerman, F.R.S., at Wye College, Swanley Hall, near Ashford, Kent, on Thursday, May 10, at 8 p.m.

Professor A. Fessard (Collège de France) will deliver three Special University Lectures in the physiology theatre of University College, Gower Street, W.C., on May 16, 21, and 22, at 5.30 p.m. In his first lecture Professor Fessard will discuss "Studies in Comparative Electrophysiology"; in the second "The Nervous Control of Electric Organs"; and in the third "The Muscle Spindle."

Professor D. Bovet (Rome) will deliver a Special University Lecture on "Natural and Synthetic Sympatholytic Drugs and their Structural Relationship with Sympathomimetic Substances" in the physiology theatre of University College, Gower Street, W.C., on Friday, May 18, at 5.30 p.m.

The Hobhouse Memorial Lecture will be delivered by Professor Charles Singer at the London School of Economics and Political Science, Houghton Street, Aldwych, W.C., on Tuesday, May 22, at 5 p.m.

Two Special University Lectures on "Oligophrenia Phenylpyruvica" will be delivered by Professor A. Fölling (Oslo) at University College Hospital Medical School, University Street, Gower Street, London, W.C., on Monday and Tuesday, May 28 and 29, at 5.30 p.m.

Dr. Jacques Le Beau (Paris) will deliver a lecture on "Neurosurgical Difficulties in Performing Limited Prefrontal Operations" at the Institute of Psychiatry, Maudsley Hospital, Denmark Hill, London, S.E., on Thursday, May 31, at 3 p.m.

A lecture on "Uraemia," arranged by the Institute of Urology, will be delivered by Professor M. L. Rosenheim at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C., on Thursday, June 7, at 5 p.m.

Professor Torsten Sjogren (Stockholm) will deliver a lecture on "Hereditary Neurologic Diseases associated with Certain Eye Diseases" at the Institute of Neurology, National Hospital, Queen Square, London, W.C., on Tuesday, June 12, at 5 p.m., and a lecture on "The Heredity of Pick's Disease and Other Presenile Conditions" at the Institute of Psychiatry, Maudsley Hospital, Denmark Hill, London, S.E., on Wednesday, June 13, at 3 p.m.

A Lecture on "Brain Abscess" will be delivered by Dr. Joe Pennybacker at the Institute of Neurology, National Hospital, Queen Square, London, W.C., on Tuesday, June 26, at 5 p.m.

Professor René Leriche (Paris) will deliver a lecture on "The Treatment of Cerebral Embolism and Thrombosis" at the Institute of Neurology, National Hospital, Queen Square, London, W.C., on Tuesday, July 3, at 5 p.m.

A lecture on "Intrathecal Tuberculin Reactions" will be delivered by Dr. Honor M. V. Smith at the Institute of Neurology, National Hospital, Queen Square, London, W.C., on Thursday, July 5, at 5 p.m.

### UNIVERSITY OF EDINBURGH

A course of lectures on "Trends and Fashions in Medicine, Their Influence and Significance" will be conducted by Dr. Douglas Guthrie in the physiology class-room of the University of Edinburgh on April 30, May 7, 14, 23, 28, June 4, 11, and 18, at 5 p.m. The lectures are free to all matriculated students and to the staff and graduates of the University, and to others on the payment of a fee of 10s. in lieu of matriculation.

## Medical News

### Special Rations and Priorities for Invalids

The Ministry of Food announces the publication of a revised memorandum, known as Med. 2 (1950), which is to replace Med. 2 (Revised 1948). Copies can be obtained from local food offices. The old milk codes have been retained for those diseases which carried entitlement to foods other than milk, except for ulcers, gastrostomy, dysentery, and typhoid fever, where the former egg codes have been retained. There is also a new item: patients suffering from hypertension who are being treated with the Kempner rice diet may now be allowed three extra rations of sugar a week on cancellation of their bacon, cheese, and fat rations.

### King Edward VII's Hospital for Officers

At the request of King Edward's Hospital Fund a consulting staff has been appointed to King Edward VII's Hospital for Officers, Sister Agnes Foundation, Beaumont Street, London, W.1. But the council of the hospital are anxious that the hospital continue to be used by specialists and practitioners not on the staff, and they have laid down that patients may be admitted under any medical practitioner of their own choice. The hospital is now for serving, retired, and ex-temporary officers of the Forces, and the fees are from 7 to 15 guineas a week according to the nature of the accommodation and certain subscription rights of patients.

### Kathleen Schlesinger Fellowship

The Medical Research Council invites applications for this whole-time fellowship for "investigating the origin and nature of cysts of the brain whether arising from tumours or not, or (for) such studies of other conditions of the central nervous system as the council may from time to time permit." Preference will be given to candidates who elect to work on the mechanisms underlying degenerative processes affecting the brain, tenable ordinarily at the National Hospital, Queen Square, London, W.C.1. The fellowship is worth £700–£1,000 per annum, according to qualifications and research experience, and is given for one year in the first instance, renewable annually twice. Applications, giving full personal particulars, an outline of the proposed research, and the names of two referees, should be lodged with the secretary, Medical Research Council, 38, Old Queen Street, London, S.W.1, not later than May 31.

### Charges for Dentures and Glasses

Under the National Health Service Bill, 1951, published on April 17, which applies both to England and Wales and to Scotland, the patient will be charged £4 5s. for full upper and lower dentures and a lower amount for single dentures. For spectacles the charge will be £1 a pair, plus the cost of the frames, which ranges from 3s. 4d. to 15s. 1d. The charges will be paid by the patient to the dentist or optician under the family practitioner services (or to the hospital authorities), and the fee payable by the executive council to the dentist or optician will be correspondingly reduced.

### Freedom of Finchley

Dr. Adam Annand Turner was made a Freeman of the Borough of Finchley at a special meeting of the Borough Council held on March 10 in recognition of his 25 years' service as Medical Officer of Health of Finchley.

### Eire Minister of Health Resigns

It is reported from Dublin that Dr. Noel Browne, Minister of Health, has resigned as a result of considerable opposition to his scheme proposing to give free medical treatment to all mothers and children. The Irish Medical Association was responsible for most of the controversy, because it objected to the principle of a medical service without a means test, and the Irish Roman Catholic hierarchy stated that the scheme was opposed to Catholic teaching. The Trade Union movement, on the other hand, strongly supported Dr. Browne. The Minister agreed to postpone for a few days his decision to resign, to allow time for further attempts to reach agreement, but these were unsuccessful. In a personal statement to the Dail Dr. Browne said that he accepted the decision of the Catholic hierarchy, but at the same time he could not introduce a scheme subject to a means test. Dr. Browne qualified in 1940 at Trinity College, Dublin, and has been interested in tuberculosis.

### Awards to Blood Donors

On April 3 the Princess Royal appealed for more blood donors when she presented awards at the Royal College of Surgeons to 65 men and 16 women who had given more than 50 donations of blood. She was received by Mr. H. Marquand, Minister of Health, who said that the service was now highly organized, and that when a national register was ready it would be possible to find the name and address of a donor with one of the rarer types of blood in a matter of minutes. The need for more donors was stressed by both the Princess and Sir Cecil Wakeley, President of the Royal College of Surgeons.

### Fifty Years Ago

It is just fifty years since Dr. J. Takamine published (in the *Therapeutic Gazette*, April 15, 1901) the first report on the isolation and properties of adrenaline in the crystalline state, a work which he had accomplished at the Parke, Davis Laboratory in New York. The son and grandson of medical men, Takamine was one of the first graduates in chemistry of the Imperial University of Japan. He came to Glasgow to work for a time on the chemistry of brewing (discovering taka-diastase), and returned to Japan in 1881 at the age of 27 to be head of the Japanese Department of Agriculture and Commerce. A few years later he married an American woman, and subsequently (1890) moved to the United States, where he became associated with Parke, Davis and Co. The active principle of the adrenal medulla was at that time a subject of great research interest in both Europe and America, but Takamine was the first to solve the chemical problem involved and to identify the hormone.

### In Brief

Dr. William Brown, formerly Wilde Reader in Mental Philosophy at Oxford, has been elected president of the British Psychological Society for the year 1951–2.

## COMING EVENTS

### Croonian Lectures

Dr. T. Fortescue Fox will deliver the Croonian Lectures before the Royal College of Physicians of London, Pall Mall East, S.W., on Tuesday, May 8, and Wednesday, May 16, at 5 p.m. His subject is "Professional Freedom."

### Institute of Biology

A symposium on "Freeze-drying" will be held in London on June 29 and 30. Provisional arrangements include sessions on the drying of bacteria and antibiotics (chairman, Sir Alexander Fleming), the drying of viruses and vaccines (chairman, Dr. C. H. Andrewes), and the drying of tissues and tissue sections (chairman, Professor J. F. Danielli). Attendance is open to all interested on application to the General Secretary, Institute of Biology, Tavistock House South, Tavistock Square, W.C.1.

## SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

#### Friday

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At Royal Free Hospital School of Medicine, 8, Hunter Street, Brunswick Square, London, W.C., April 20, 8.30 p.m., "*Some Important Clinical Aspects of Modern Bacteriology*," by Dr. Anne Gibson.

#### Monday

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—April 23, 5.30 p.m., "*Certain Congenital Ocular Palsies*," by Mr. A. B. Nutt.

MEDICAL SOCIETY OF LONDON, 11, Chandos Street, Cavendish Square, W.—April 23, 8.30 p.m., discussion: "*The Effects of Tobacco Smoking*," to be introduced by Professor J. H. Burn, F.R.S., and Dr. W. R. Doll.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—April 23, 5 p.m., "*Inguinal Failure*," by Mr. W. J. Lytle; 6.15 p.m., "*Renal Failure*," by Mr. R. W. Reid.

ROYAL EYE HOSPITAL St. George's Circus, Southwark, London, S.E.—April 23, 5 p.m., "*Detachment of the Retina*," by Professor Arnold Sorsby.

#### Tuesday

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—April 24, 5 p.m., "*Arthritis of the Hip*," by Mr. W. A. Law; 6.15 p.m., "*Bone Grafting*," by Mr. H. Osmond-Clarke.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—April 24, 5 p.m., "*Astigmatism. Factors Affecting Binocular Vision: Convergence*," by Dr. T. H. Whittington.

WESTMINSTER SCHOOL OF MEDICINE, Meyerstein Lecture Theatre, Horseferry Road, London, S.W.—April 24, 5 p.m., clinico-pathological meeting. Discussion: "*Influenza*."

#### Wednesday

GLASGOW UNIVERSITY: DEPARTMENT OF OPHTHALMOLOGY.—April 25, 8 p.m., "*Emotions and Eye Disease*," by Professor W. J. B. Riddell.

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—April 25, 5.30 p.m., "*Electro-Physiology of the Retina*," by Dr. L. C. Thomson. (Demonstration in three groups on May 2.)

●RENAL ASSOCIATION.—At Wellcome Research Institute, 183, Euston Road, London, N.W., April 25, 4.30 p.m., coloured film: "*Kidney in Health and Disease*."

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—April 25, 5 p.m., "*The Management of Intestinal Obstruction*," by Professor F. A. R. Stammers; 6.15 p.m., "*Infections of the Hand*," by Mr. E. C. B. Butler.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—April 25, 5 p.m., "*Buphthalmos*," by Mr. R. P. Crick.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, London, W.—April 25, 3.30 p.m., "*Hypnotism—Its Uses and Limitations in Medicine*," by Dr. Henry Yellowlees.

#### Thursday

EDINBURGH UNIVERSITY, University New Buildings (Anatomy Theatre), Teviot Place, Edinburgh.—April 26, 5 p.m., "*Vitamin $B_{12}$ and Folic Acid in the Megaloblastic Anaemias*," Honyman Gillespie Lecture by Dr. R. H. Girdwood.

MEDICO-LEGAL SOCIETY.—At 26, Portland Place, London, W., April 26, 8.15 p.m., "*The Medico-Legal Significance of Death Following Abortion*," by Dr. R. Donald Teare.

●RENAL ASSOCIATION.—At Ciba Foundation, 41, Portland Place, London, W., April 26, 4.30 p.m., *"The Kidney and the Circulatory System,"* by Professor K. J. Franklin; *"Spinal Anaesthesia and the Kidney,"* by Dr. A. H. Galley; *"Renal Changes in Obstetric Shock,"* by Dr. A. D. Telford Govan.

ROYAL ARMY MEDICAL COLLEGE, Millbank, London, S.W.—April 26, 5 p.m., *"Biting Insects in the North,"* by Major R. A. Smart.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—April 26, 3.45 p.m., *"Experimental Study of the Course and Regulation of Neoplasia,"* Imperial Cancer Research Fund Lecture by Dr. L. Foulds.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—April 26, 5 p.m., *"Peripheral Nerve Injuries,"* by Mr. H. J. Seddon; 6.15 p.m., *"Aneurysms of the Carotid Vessels,"* by Professor Lambert Rogers.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—April 26, 5.30 p.m., *"Ocular Therapeutics,"* by Miss J. M. Dollar.

ST. ANDREWS UNIVERSITY.—At Lecture Theatre, Materia Medica Department, Medical School, Small's Wynd, Dundee, April 26, 5 p.m., *"Some Circulatory Changes in Surgical Conditions,"* by Professor W. C. Wilson.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—April 26, 4.30 p.m., *"Neurology,"* lecture-demonstration.

TORQUAY AND DISTRICT MEDICAL SOCIETY.—At Torbay Hospital, April 26, 8.30 p.m., *"The Changing Face of Midwifery,"* by Mr. Alan Brews.

UNIVERSITY COLLEGE, Physiology Theatre, Gower Street, London, W.C.—April 26, 4.45 p.m., *"Energy Transformations in Living Matter,"* by Professor H. A. Krebs.

UNIVERSITY OF WALES: WELSH NATIONAL SCHOOL OF MEDICINE.—At Reardon Smith Lecture Theatre, Park Place, Cardiff, April 26, 8 p.m., *"Child Health,"* by Professor A. G. Watkins.

**Friday**

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—April 27, 5.30 p.m., *"Sensitivity of Ocular Structures,"* by Professor D. Slome.

KENT AND CANTERBURY HOSPITAL, Canterbury.—April 27, 8 p.m., clinical meeting.

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES, 11, Chandos Street, London, W.—April 27, 7.15 for 8 p.m., general meeting. *"The Use of Penicillin in the Treatment of Neurosyphilis,"* by Dr. W. D. Nicol and Dr. Maeve Whelen. A discussion will follow.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—April 27, 5 p.m., *"Ulcerative Colitis,"* by Mr. R. S. Corbett; 6.15 p.m., *"Post-gastrectomy Syndromes,"* by Mr. N. C. Lake.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—April 27, 4.30 p.m., *"Surgery of Cataract,"* by Mr. A. J. Cameron.

## BIRTHS, MARRIAGES, AND DEATHS

### BIRTHS

**Bindon Blood.**—On April 11, 1951, at Middlesex Hospital, London, W., to Rita, wife of W. Bindon Blood, M.B., B.S., a son—Nigel Bindon.

**Freeman.**—On April 12, 1951, at Royal Infirmary, Cardiff, to Florence Eleanor (formerly Thomas), wife of Dr. A. G. Freeman, a son—Michael John.

**Sutton.**—On April 7, 1951, at the Norfolk and Norwich Hospital, to Catherine, wife of Dr. P. H. Sutton, a daughter.

**Swinscow.**—On April 12, 1951, to Josephine, wife of Dr. Douglas Swinscow, a daughter.

### MARRIAGES

**Medine—Cortell.**—On April 1, 1951, at Boston, Mass., U.S.A., Dr. Myer Medine, M.B.E., Lieutenant-Colonel, R.A.M.C., retired, to Dr. Ruth E. Cortell.

**Taylor—Tebbs.**—On March 22, 1951, at St. Michael's Church, Highgate, London, N., R. S. Taylor, O.B.E., M.R.C.S., L.R.C.P., F.D.S., to Mary Angela Tebbs.

### DEATHS

**Cross de Chavannes.**—On April 1, 1951, at The Court House, West Meon, Hants, Edward Henry Eustace Cross de Chavannes, M.D., Wing Commander, R.A.F., retired.

**Douglas.**—On March 31, 1951, at his home, 39, Greenock Road, Largs, Ayrshire, Archibald Randolph Fulton Douglas, L.R.C.P.&S.Ed., L.D.S., D.D.S.

**Fawcett.**—On April 6, 1951, at Conger House, Toddington, Beds, Ralph Frankland Morris Fawcett, D.S.O., M.D., J.P., Lieutenant-Colonel, R.A.M.C., retired.

**Harrison.**—On March 28, 1951, at Leicester Royal Infirmary, Louis Kenneth Harrison, C.B.E., M.B., B.Ch., of Springfield House, Leicester, aged 79.

**Heath.**—On April 2, 1951, at Moretonhampstead Cottage Hospital, Devon, Oliver Heath, M.D., aged 73.

**Robinson.**—On April 1, 1951, James Salmond Robinson, M.B., F.R.C.S.Ed., of Cheltenham.

**Rundall.**—On April 7, 1951, at Broxbourne, Laurence Rundall, M.B., Ch.B., Captain, I.M.S., retired, of Kerri Cottage, Cooden Beach, Sussex.

**Salvage.**—On April 5, 1951, John Valentine Salvage, M.D., Lieutenant-Colonel, R.A.M.C., retired, of 52, Burleigh Mansions, London, W.C.

**Schuster.**—On March 29, 1951, Eugen Richard Schuster, M.D., of 27, Shirehall Park, London, N.W.

**Scott.**—On April 5, 1951, at Bristol Royal Infirmary, Harold Hope Scott, L.R.C.P.&S.Ed., L.R.F.P.S., of Linden Gate, Clifton Down Road, Bristol.

**Siddons.**—On April 5, 1951, at Trosnant Lodge, Pontypool, Mon., Bertram Siddons, M.B., Ch.B., aged 57.

# Any Questions?

*Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.*

### Antivitamins

**Q.**—*What are antivitamins? Are they important in human nutrition?*

**A.**—Strictly speaking, antivitamins are defined as substances which counteract the action of vitamins by biological competition resulting from similarities in chemical constitution. Thus the sulphonamide drugs may be considered to be antivitamins in opposing the action of the vitamin *para*-aminobenzoic acid. Numerous artificial antivitamins opposing most of the B vitamins and vitamin K have been synthesized. When they are given to animals it is necessary to raise considerably the allowance of the corresponding vitamin in order to avoid symptoms of deficiency. An excellent example of a natural antivitamin may be seen in the dicoumarol of spoilt sweet clover, which causes haemorrhages in farm animals by opposing vitamin K.

In a less strict sense the term antivitamin may be extended to include "toxamins" which oppose the action of vitamins by mechanisms which are not related to biological competition, or at least have not been proved to be so related. Thus raw egg-white contains a factor called "avidin" which inactivates biotin in rats, raw fish precipitates the onset of acute vitamin $B_1$ deficiency in foxes, and bracken causes the same deficiency in farm animals.

In human nutrition at least one antivitamin, the phytic acid of cereals, is of great importance. It is a phosphorylated form of inositol, and opposes the action of vitamin D. When the recent war necessitated the use of our present coarse flour for making bread the danger that an increased intake of phytic acid might cause rickets was recognized, and calcium carbonate has been added to the flour as a precautionary measure ever since.

### Syphilis in Different Races

**Q.**—*To what extent do racial factors determine the clinical manifestations of syphilis?*

**A.**—In the American negro, as compared with the white races, pustular and annular eruptions (precocious tertiarism) and generalized adenitis are much more frequently observed during the secondary phase of the disease. In late syphilis bone lesions and cardiovascular complications are also more common, but tabes dorsalis and general paralysis of the insane are much less frequent. (This latter is also true of the Chinese, though the Japanese in this respect are similar to Europeans.) It has also been stated that visceral syphilis is not observed in the African negro, and that extra-genital chancres are uncommon.

There are many who maintain that the Pacific islanders and natives of other tropical countries in which yaws is endemic develop, following an attack, an immunity to syphilis. This may also be true of Bedouins who have contracted bejel, another disease due to a spirochaete morphologically indistinguishable from *T. pallidum*. Syphilis has rarely been reported among the Polynesians of Fiji (in whom yaws is especially prevalent), though it is widespread among the Indian and half-caste population of the island. As against this many experiments on human beings and monkeys have all shown that a successful inoculation of yaws produces no immunity against syphilis and vice versa. The situation is obscured by the confusion that still exists between syphilis, yaws, and bejel, but the recently evolved treponema immobilization test may help to clarify it.

### Sexual Desire in the Middle-aged

**Q.**—*I have recently been consulted by two men, each aged 50 and each complaining of diminution of sexual desire coming on fairly rapidly over a period of about six months. Both are happily married and otherwise healthy. Both complain of inability to maintain or initiate a satisfactory erection. Is this normal at this age, or likely to be permanent, and is there any treatment?*

**A.**—The duration of sexuality varies greatly in different men, some retaining it into the seventies, and occasionally even into the eighties, and others losing sexual interest even in the early fifties. In the latter case it is unlikely that sexuality has ever been very strong, so that the frequency of intercourse gradually drops until it ceases altogether after 20 years of married life. In the two cases quoted it is important to make sure that neither physical nor psychological causes for the absence of desire exist—such as glycosuria, fatigue from overwork, domestic emotional difficulties, etc. Methyl testosterone is often given in such cases by mouth, but it is not usually effective, and, when it is effective, this is often the result of suggestive action. Small doses of thyroid have also been known to help.

### Prematurity, Jaundice, and the Rh Factor

**Q.**—*A patient at the age of 25 had albuminuria during a pregnancy. The child was three weeks premature, jaundiced at birth, and died in two weeks. Two years later she had a further pregnancy, again with signs of moderate toxaemia, and again the child was three weeks premature (weight 5 lb. 2 oz.—2.3 kg.) and deeply jaundiced. This child survived and is now healthy. The patient is again pregnant. She and her husband are both Rh negative. (1) Are there any steps I should take to prevent a possible recurrence of the first mishap? (2) Has the Rh factor any bearing on the presence of the toxaemia?*

**A.**—(1) If a husband and wife are both Rh negative, all their children must be Rh negative, and such children cannot immunize the mother to the Rh factor. It is, of course, possible for a woman to become immunized to other blood-group factors and for this to be the cause of mishaps during pregnancy. But these cases are rare and should be considered only when there is clinical evidence that one or more infants have been affected with haemolytic disease in one of its recognized clinical forms.

In the present case two infants have been born prematurely and both have been jaundiced. Jaundice in premature infants is so common that by itself it should hardly arouse a suspicion of a haemolytic process. The first child is said to have been jaundiced at birth. It is very important to know whether this means jaundiced at the moment of birth or jaundiced within two or three days of birth. If the infant was actually jaundiced when it was born, the suspicion of haemolytic disease of the newborn becomes strong. In that case determination of the ABO groups of the husband and his wife might be informative. Occasionally, when the mother is group O and the father belongs to group A or B, the infants inheriting A or B from the father become affected by the anti-A or anti-B in the mother's serum and suffer from a form of haemolytic disease of the newborn. If, in the present case, the husband and wife both belong to the same ABO group, this possibility would be excluded and it would then be worth sending the mother's serum to a blood-group reference laboratory so that an examination could be made for unusual antibodies, apart from anti-D (the common kind of anti-Rh).

(2) There does not seem to be any close connexion between toxaemia of pregnancy and iso-immunization. In the present state of knowledge the development of toxaemia in the mother should be regarded as coincidence.

### Skin Tests in Tuberculosis Contacts

**Q.**—*Following exposure to infection from a patient suffering from open pulmonary tuberculosis, five children in the household were recently patch-tested by me, using prepared patches of human, bovine, and control type. All the reactions were negative, with the exception of one child, aged 4 years, who showed marked reaction to the bovine patch only. The child had had a mild attack of German measles about 18 days previously, but is apparently healthy. What interpretation am I to put upon this positive reaction, and what further investigation would you advise?*

**A.**—There is often cross-reaction between the bovine and human tuberculin patch tests. The solitary positive with bovine patch may or may not be significant. As a confirmation a Mantoux test with 1/10,000 old tuberculin should be done: 0.1 ml. is injected intradermally and the result read in 48 hours; a weal of diameter greater than 5 mm. indicates a positive reaction. If this reaction is negative the test should be repeated using 1/1,000 old tuberculin. In a case of this kind there is little point in carrying the reaction to a higher concentration if the 1/1,000 is negative. As a doubt has been raised by the patch test it is certainly wise to have a radiograph of the child's chest.

It must be remembered that even if the skin tests in all the children are negative they should be repeated at three-monthly intervals for at least a year, or, if contact continues, indefinitely. For these tests it is preferable to use tuberculin jelly. The skin over the sternum or between the scapulae is cleaned with anaesthetic ether or acetone, and a little jelly applied. It is covered with "elastoplast" and the test is read in 48 hours. Any weal, papule, or vesicle at the site of the application of the jelly indicates a positive reaction. For children over 5 the test is made more sensitive by giving the skin a single gentle stroke with "flour paper" before applying the jelly.

### Control of Growth

**Q.**—*What factors affect growth in height in human beings? Is there any means of stimulating the rate of growth?*

**A.**—The pituitary gland, in particular the pituitary eosinophil cells, appears to be the primary endocrine factor determining growth, although this in its turn is genetically determined. Although the growth hormone has its specific growth-stimulating effect on epiphysial cartilage quite independently of other hormones, it is recognized that the other endocrine glands, particularly the adrenals, thyroid, and gonads, play a part. Albright postulates two physiological phases of growth, the first before puberty, due to the pituitary growth hormone associated with a high serum phosphorus; and the second after puberty, associated with secretion of the gonads. Thyroid will stimulate growth in a cretin and sometimes in idiopathic dwarfism. Testosterone will stimulate growth in hypogonadism—for example, in infantilism—and there is evidence that given clinically it causes premature union of the epiphyses, as happens in pathological sexual precocity and in animal experiments.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 2111. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

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